MOUNT SINAI EXPERT GUIDES

Critical Care

- Potential pitfalls / common mistakes
- Clinical pearls
- Management algorithms
- Evidence-based guidelines

EDITED BY
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Series Foreword

Now more than ever, immediacy in obtaining accurate and practical information is the coin of the realm in providing high quality patient care. The Mount Sinai Expert Guides series addresses this vital need by providing accurate, up-to-date guidance, written by experts in formats that are accessible in the patient care setting: websites, smartphone apps, and portable books. The Icahn School of Medicine, which was chartered in 1963, embodies a deep tradition of pre-eminence in clinical care and scholarship that was first shaped by the founding of the Mount Sinai Hospital in 1855. Today, the Mount Sinai Health System, comprised of seven hospitals anchored by the Icahn School of Medicine, is one of the largest health care systems in the United States, and is revolutionizing medicine through its embracing of transformative technologies for clinical diagnosis and treatment. The Mount Sinai Expert Guides series builds upon both this historical renown and contemporary excellence. Leading experts across a range of disciplines provide practical yet sage advice in a digestible format that is ideal for trainees, mid-level providers, and practicing physicians. Few medical centers in the United States could offer this type of breadth while relying exclusively on its own physicians, yet here no compromises were required in offering a truly unique series that is sure to become embedded within the key resources of busy providers. In producing this series, the editors and authors are fortunate to have an equally dynamic and forward-viewing partner in Wiley Blackwell, which together ensures that health care professionals will benefit from a unique, first-class effort that will advance the care of their patients.

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Preface

This book, as part of the Mount Sinai Expert Guide series, aims to guide clinicians who care for patients in critical care units. Our goal is for the clinician – whether student, trainee, or faculty – to use this book when faced with a critically ill patient in order to understand the physiology, evaluation, and management of disease.

In conjunction with the founding of Mount Sinai's Institute for Critical Care Medicine in 2017, we have brought together experts from the Mount Sinai Health System to provide the most current knowledge of management for these complex disorders. We hope that the information and management protocols will be utilized at the bedside, and will inspire the reader to delve into the medical literature, discover, and provide the highest quality care for their patients.

We are grateful to our patients, colleagues, and teachers. We hope that our book will advance patient care, and the learning and sharing of knowledge in medicine.

Janet M. Shapiro and Stephan A. Mayer

Abbreviations

2D	two-dimensional
3D	three-dimensional
AAA	abdominal aortic aneurysm
AABB	American Association of Blood Banks
ABG	arterial blood gas
AC	anticoagulation
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACLS	advanced cardiac life support
ACS	abdominal compartment syndrome; acute coronary syndrome/s; American College of Surgeons
ADC	apparent diffusion coefficient
ADH	antidiuretic hormone
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
AED	antiepileptic drug; automated external defibrillator
AF	atrial fibrillation
AFE	amniotic fluid embolism
AFl	atrial flutter
AG	anion gap
AHA	American Heart Association
AHF	acute hepatic failure
AIDS	acquired immune deficiency syndrome
AIN	acute interstitial nephritis
AIS	acute ischemic stroke
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AMAE	acute mesenteric arterial embolism
AMAT	acute mesenteric arterial thrombosis
AMI	acute mesenteric ischemia
AML	acute myeloid leukemia
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANP	atrial natriuretic peptide
AoV	aortic vein
AP	anteroposterior
APACHE	Acute Physiologic Assessment and Chronic *Health* Evaluation (score)
APRV	airway pressure release ventilation
aPTT	activated partial thromboplastin time
ARAS	ascending reticular activating system
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
ART	antiretroviral therapy
ASA	American Society of Anesthiologists
ASCVD	atherosclerotic *cardiovascular disease*
ASIA	American Spinal Injury Association
ASP	antimicrobial stewardship program
AST	aspartate aminotransferase
AT	atrial tachycardia
ATLS	advanced traumatic life support
ATN	acute tubular necrosis
ATP	adenosine triphosphate
ATS	American Thoracic Society
AUC	area under curve
AV	atrioventricular
$AVDO_2$	arteriovenous difference in oxygen content
AVF	*arteriovenous fistula*
AVM	arteriovenous malformation
AVNRT	atrioventricular nodal re-entrant tachycardia
AVRT	atrioventricular re-entrant tachycardia
BAL	bronchoalveolar lavage
BBB	blood–brain barrier
BEAR	brainstem evoked audio response
BG	blood glucose
BIPAP	bilevel positive airway pressure
BIS	bispectral index
BLS	basic life support
BMI	body mass index
BMP	basic metabolic profile/panel
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute
BPS	behavioral pain scale
BSA	body surface area

BSAS	bedside shivering assessment scale
BUN	blood urea nitrogen
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAP	community-acquired pneumonia
CAPC	Center to Advance Palliative Care
CAS	carotid artery stenosis
CAUTI	catheter-associated urinary tract infection
CBC	complete blood count
CBF	cerebral blood flow
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CEA	carotid endarterectomy
cEEG	continuous electroencephalogram
cfu	colony-forming unit
CFV	common femoral vein
CHF	congestive heart failure
CI	cardiac index
CIM	critical illness myopathy
CIN	contrast-induced nephropathy
CIP	critical illness polyneuropathy
CK	creatine kinase
CKD	chronic kidney disease
CLABSI	central line-associated bloodstream infection
CML	chronic myeloid leukemia
CMP	comprehensive metabolic profile
$CMRO_2$	cerebral metabolic rate of oxygen consumption
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system
CO	cardiac output
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPE	cardiogenic pulmonary edema
CPM	central pontine myelinolysis
CPOT	critical care pain observation tool
CPP	cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
Cr	creatinine
CRE	carbapenem-resistant Enterobacteriaceae
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
C/S	culture and sensitivity
CSE	convulsive status epilepticus
CSF	cerebrospinal fluid
CSHT	context-sensitive half-time
CT	computed tomography
CTA	computed tomography angiogram/angiography
CVA	cerebrovascular accident
CVP	central venous pressure
CVR	cerebrovascular resistance
CVVH	continuous veno-venous hemofiltration
CVVHD	continuous veno-venous hemodialysis
CVVHDF	continuous veno-venous hemodiafiltration
CXR	chest X-ray
D5W	5% dextrose in water
D50W	50% dextrose in water
DALYs	disability-adjusted life years
DAPT	dual antiplatelet therapy
DC	direct current
DCI	delayed cerebral ischemia
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
DNI	do not intubate
DNR	do not resuscitate
DOAC	direct oral anticoagulant
DP	peritoneal dialysis
2,3-DPG	2,3-diphosphoglycerate
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders 5*
DTI	direct thrombin inhibitors
DVT	deep vein thrombosis
DWI	diffusion weighted imaging
EBV	Epstein–Barr virus
$ECCO_2R$	extracorporeal carbon dioxide removal
ECF	extracellular fluid
ECG	electrocardiography/electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EEG	electroencephalography/electroencephalogram
EIA	enzyme immunoassay
EMS	emergency medical service
EPAP	end-expiratory positive airway pressure
ER	emergency room

ESBL	extended-spectrum beta-lactamase
ESICM	European Society of Intensive Care Medicine
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ET	endotrachea
$ETCO_2$	end-tidal carbon dioxide
ETT	endotracheal tube
EVD	external ventricular drainage
F	femoral
FAST	focused assessment using sonography for trauma
FDA	Food and Drug Administration (USA)
FeNa	fractional excretion of sodium
FeUrea	fractional excretion of urea
FFP	fresh frozen plasma
FiO_2	fractional inspired oxygen
FLAIR	fluid attenuated inversion recovery
FMT	fecal microbiota therapy
FP24	frozen plasma (within 24 hours)
FRC	functional residual capacity
FVC	forced vital capacity
GABA	gamma-aminobutyric acid
GBS	Guillain–Barré syndrome
GCS	Glasgow Coma Scale
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GI	gastrointestinal
GINA	Global Initiative for Asthma
GM-CSF	granulocyte–macrophage colony-stimulating factor
GNB	gram-negative bacilli
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
GPC	gram-positive cocci
GVHD	graft-versus-host disease
GW	guidewire
H_2	histamine-2
HAART	highly active antiretroviral therapy
HAP	hospital-acquired pneumonia
Hb	hemoglobin
HBV	hepatitis B virus
HCAP	health care-associated pneumonia
HCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
HE	hepatic encephalopathy
HELLP	hemolysis, elevated liver enzymes, low platelets (syndrome)
HFNC	high flow nasal cannula
HFPEF	heart failure with preserved ejection fraction
HFREF	heart failure with reduced ejection fraction
Hib	*Haemophilus influenza* type b
HIDA	hepatobiliary iminodiacetic acid
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
HSV	herpes simplex virus
HT	hemorrhagic transformation
HUS	hemolytic uremic syndrome
IA	intra-arterial
IABP	intra-aortic balloon pump
IAH	intra-abdominal hypertension
IAP	intra-abdominal pressure
IBW	ideal body weight
ICD	implantable cardioverter defibrillator
ICF	intracellular fluid
ICH	intracerebral hemorrhage
ICP	intracranial pressure
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
Ig	immunoglobulin
IHD	intermittent hemodialysis
IJ	internal jugular
IJV	inferior jugular vein
IL	interleukin
ILCOR	International Liaison Committee on Resuscitation
ILD	interstitial lung disease
IMV	invasive mechanical ventilation
INR	international normalized ratio
IO	intraosseous
IPAL-ICU	Improving Palliative Care in the ICU
IPAP	inspiratory positive airway pressure
IPF	idiopathic pulmonary fibrosis
IRIS	immune reconstitution inflammatory syndrome
ISS	injury severity score
IV	intravenous
IVAC	infection-related ventilator-associated complication
IVC	inferior vena cava
IVIg	intravenous immunoglobulin

JVP	jugular venous pressure
KCl	potassium chloride
LAD	left anterior descending (artery)
LBBB	left bundle branch block
LD	loading dose
LDF	laser Doppler flowmetry
LDH	lactate dehydrogenase
LDL	low density lipid
LDUH	low dose unfractionated heparin
LFT	liver function test
LiDCO	lithium dilution cardiac output
LKM	liver–kidney microsomal (antibody)
LLQ	left lower quadrant
LMA	laryngeal mask airway
LMW	low molecular weight
LMWH	low molecular weight heparin
LOC	loss of consciousness
LOS	length of stay
LP	lumbar puncture
LPR	lactate : pyruvate ratio
LSD	lysergic acid diethylamide
LV	left ventricular/ventricle
LVAD	left ventricular assist device
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
LVO	large vessel occlusion
LVOT	left ventricular outflow tract
MAC	Macintosh blade
MAHA	microangiopathic hemolytic anemia
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MASCC	Multinational Association for Supportive Care in Cancer
MAT	multifocal atrial tachycardia
MBC	minimum bactericidal concentration
MCA	middle cerebral artery
MD	doctor; maintenance dose
MDI	metered dose inhaler
MDMA	3,4-methylenedioxy-methamphetamine
MDR	multidrug resistant
MELD	model for end-stage liver disease
MI	myocardial infarction
MIC	minimum inhibitory concentration
MMF	mycophenolate mofetil
MODS	multiorgan dysfunction syndrome
MR	mitral regurgitation
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
MTP	massive transfusion protocol
MVA	motor vehicle accident
MVT	mesenteric venous thrombosis
Na	sodium
NAC	*N*-acetylcysteine
NASH	non-alcoholic steatohepatitis
NCS	Neurocritical Care Society
NCSE	non-convulsive status epilepticus
NDM-1	New Delhi metallo-beta-lactamase
NG	nasogastric
NHSN	National Healthcare Safety Network
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (trial)
NIF	negative inspiratory force
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NMDA	*N*-methyl-D-aspartate
NNT	number needed to treat
NOMI	non-occlusive mesenteric ischemia
NPH	neutral protamine Hagedorn
NPO	nil per os
NPPV	non-invasive positive pressure ventilation
NQF	National Quality Forum
NRTI	nucleoside reverse transcriptase inhibitor
NS	normal saline
1/2 NS	half normal saline
NSAIDs	non-steroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NSTE-ACS	non-ST elevation acute coronary syndromes
NSTEMI	non-ST elevation myocardial infarction
NYHA	New York Heart Association
O_2	oxygen
OHS	obesity hypoventilation syndrome
OI	opportunistic infection
OLT	orthotopic liver transplantation

OPTN	Organ Procurement Transplantation Network
OR	odds ratio; operating room
OTC	over-the-counter
PAC	pulmonary artery catheter
PaO_2	arterial oxygen pressure
$PaCO_2$	arterial carbon dioxide pressure
PAD	pulmonary artery disease
PAK	pancreas after kidney
PAWP	pulmonary artery wedge pressure
$PbtO_2$	brain tissue oxygen partial pressure
PBW	predicted body weight
PC	pressure control
PCA	patient controlled analgesia
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PCP	pneumocystis pneumonia
PCR	polymerase chain reaction
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic/peritoneal dialysis
PDT	percutaneous dilational tracheostomy
PE	pulmonary embolism
PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure
PEF	peak expiratory flow
PEG	percutaneous endoscopic gastrosotomy
PESI	Pulmonary Embolism Severity Index
PET	positron emission tomography
$PETCO_2$	peak end-tidal partial pressure of carbon dioxide
PGL	persistent generalized lymphadenopathy
PH	parenchymal hemorrhage
PI	pulsatility index
PiCCO	pulse contour cardiac output
PIP	peak inspiratory pressure
PLT	platelet
PO	per os
POC	point-of-care
POCUS	point-of-care ultrasound
PPE	parapneumonic effusion
PPI	proton pump inhibitor
PPN	partial parenteral nutrition
PRBCs	packed red blood cells
PRIS	propofol-related infusion syndrome
PRVC	pressure-regulated volume control
PS	pressure support
PSI	pneumonia severity index
PSV	pressure support ventilation
PT	prothrombin time
PTA	pancreas transplant alone
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PTX	pneumothorax
PVR	pulmonary vascular resistance
RA	right atrium
RAAS	renin–angiotensin–aldosterone system
RAP	right arterial pressure
RASS	Richmond Agitation-Sedation Scale
RBBB	right bundle branch block
RBC	red blood cell
RCA	right coronary artery
RCT	randomized controlled trial
RLL	right lower lobe
RLQ	right lower quadrant
RML	right middle lobe
RN	registered nurse
ROSC	return of spontaneous circulation
RQ	respiratory quotient
RR	respiratory rate
RRT	renal replacement therapy
RSBI	rapid shallow breathing index
RTS	Revisited Trauma Score
RUL	right upper lobe
RUQ	right upper quadrant
RUSH	rapid ultrasound in shock
RV	right ventricular/ventricle
Rx	treatment
SA	subclavian artery
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SBT	small bowel transplantation, spontaneous breathing trial
SC	subcutaneous
SCCM	Society of Critical Care Medicine
SCI	spinal cord injury
SCLC	small cell lung cancer
$ScvO_2$	central venous oxygen saturation
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIMV	synchronized intermittent mandatory ventilation
SIRS	systemic inflammatory response syndrome
$SjvO_2$	jugular venous oxygen saturation
SL	subclavian lateral; symptomatic leukostasis

SM	subclavian medial
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SNRI	serotonin-norepinephrine reuptake inhibitor
SOFA	sequential organ failure assessment (score)
SOL	signs of life
SPK	simultaneous pancreas–kidney
SpO_2	peripheral capillary oxygen saturation
SQ	subcutaneous
SSEP	somatosensory evoked potential
SSRI	selective serotonin reuptake inhibitor
ST	sinus tachycardia
ST	spontaneous timed
sTBI	severe traumatic brain injury
STE	ST elevation
STEMI	ST elevation myocardial infarction
SV	stroke volume, subclavian vein
SVCS	superior vena cava syndrome
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
SW	social worker
TACO	transfusion-associated circulatory overload
TAD	transfusion-associated dyspnea
TAH	total artificial heart
TAVR	transcatheter aortic valve replacement
TB	tuberculosis
TBI	traumatic brain injury
TBSA	total body surface area
TCA	tricyclic antidepressant
TDF	thermal diffusion flowmetry
TEE	transesophageal echocardiography/ echocardiogram
TIA	transient ischemic attack
TIPS	transjugular intrahepatic portosystemic shunt
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
tPA	tissue plasminogen activator
TPN	total parental nutrition
TRALI	transfusion-related acute lung injury
TRP	tubular reabsorption of phosphate
TSH	thyroid-stimulating hormone
TT	tracheostomy tube
TTE	transthoracic echocardiography/ echocardiogram
TTM	therapeutic temperature modulation
TTP	thrombotic thrombocytopenic purpura
TWI	T wave inversion
UA	unstable angina; urinalysis
UFH	unfractionated heparin
URI	upper respiratory infection
US	ultrasound
USPSTF	United States Preventive Services Task Force
UTI	urinary tract infection
V-A	venous-arterial
VAC	ventilator-associated condition
VAD	ventricular assist device
VAE	ventilator-associated event
VAP	ventilator-associated pneumonia
VATS	video-assisted thoracoscopy surgery
VBG	venous blood gas
VC	vital capacity
VC	volume control
VF	ventricular fibrillation
VKA	vitamin K antagonist
VME	viral meningoencephalitis
V/Q	ventilation–perfusion
VS	volume support
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
VTI	velocity time interval
V-V	veno-venous
vWD	von Willebrand disease
vWF	von Willebrand factor
VZV	varicella zoster virus
WBC	white blood cell
WFNS	World Federation of Neurosurgeons Scale
WHO	World Health Organization
WPW	Wolff–Parkinson–White

About the Companion Website

This series is accompanied by a companion website:

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The website includes:

- Case studies: 15.1, 27.1 and 29.1
- Color versions of images: 5.2, 6.4, 16.1, 36.1 and 48.1
- Links to video clips: 1.1, 3.1, 3.2, 3.3, 4.1, 4.2, 5.1, 5.2, 5.3 and 6.1
- Multiple choice questions for all chapters

In addition the following images are also available online:

Chapter 4

Online figure 4.1 (A) Pericardial effusion (Peff) short axis window transesophageal echo (TEE). (B) Pericardial effusion four chamber window transthoracic echo (TTE) demonstrating right ventricular (RV) diastolic collapse. LV, left ventricle.

Online figure 4.2 Splenorenal recess with hemothorax view. Free fluid (arrow) can be seen between the spleen and kidney.

Online figure 4.3 Kidney view. The normal hyperechoic appearance of the pelvis (arrow) below the cortex and medulla.

Online figure 4.4 Hydronephrosis. The anechoic appearance of the pelvis (arrow) below the cortex and medulla indicates dilation of the renal pelvis consistent with hydronephrosis from obstruction, e.g. nephrolithiasis.

Online figure 4.5 (A) Transverse view of abdominal aortic aneurysm (AAA). (B) Transverse view of AAA at level of dissection. (Courtesy of Richard Stern, MD, Mount Sinai Hospital.)

Chapter 5

Online figure 5.1 Tracheostomy bedside insertion, showing a dilator above the tracheal ring.

Chapter 13

Online figure 13.1 HeartWare centrifugal flow device.

Online figure 13.2 Syncardia total artificial heart.

Chapter 24

Online figure 24.1 Barotrauma in a patient with status asthmaticus. Patient has extensive subcutaneous emphysema and required chest tubes for bilateral pneumothorax.

PART 1

Basic Techniques and Procedures

Section Editor: John M. Oropello

CHAPTER 1

Airway Management

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OVERALL BOTTOM LINE

- Airway management is a vital life-saving skill for the ICU provider.
- The provider should be capable of using a broad range of devices including endotracheal tubes, supraglottic devices, and direct and video laryngoscopes.
- Understanding airway anatomy, performing a thorough airway examination, and recognizing potential challenges of both bag-mask ventilation as well as endotracheal intubation are essential.
- Formulating a plan (often with a backup in mind), proper monitoring, meticulous attention to patient positioning, and immediate availability of equipment and medications are necessary to provide safe and effective care.
- It is crucial to know when to call for assistance, when to attempt a 'rescue technique,' and when escalation to invasive airway management (i.e. cricothyrotomy or tracheostomy) is necessary.

Functional anatomy of the upper airway

- The human airway consists of two openings: the nose, which leads to the nasopharynx, and the mouth, which leads to the oropharynx. These passages are separated anteriorly by the palate and they join posteriorly, although still separated via an imaginary horizontal line extending posteriorly from the palate. Inferiorly past the base of the tongue, the epiglottis separates the oropharynx from the laryngopharynx, or hypopharynx. The epiglottis serves to protect against aspiration by covering the opening of the larynx (the glottis) during swallowing. The larynx is a cartilaginous skeleton comprised of nine cartilages as well as ligaments and muscles. The thyroid cartilage functions partly to shield the vocal cords. Inferior to the cricoid cartilage lies the trachea, which extends to the carina at approximately T5 where it branches into the right and left mainstem bronchi. The right mainstem bronchus takeoff is more straight and vertical, making it the most likely path taken by a deep endotracheal tube placement.
- Innervation of the upper airway is from the cranial nerves. Sensation to mucous membranes of the nose is supplied by the ophthalmic division (V1) of the trigeminal nerve anteriorly and the maxillary division of the same nerve posteriorly. The glossopharyngeal nerve provides sensation to the posterior third of the tongue as well as the tonsils and undersurface of the soft palate.
- Below the epiglottis, sensation is supplied by branches of the vagus nerve. The superior laryngeal branch divides into external and internal segments. The internal branch provides sensation to the larynx between

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the epiglottis and the vocal cords. Another branch of the vagus nerve, the recurrent laryngeal nerve, provides laryngeal sensation below the vocal cords as well as the trachea.

- Motor supply to the muscles of the larynx is from the recurrent laryngeal nerve, with the exception of the cricothyroid muscle (vocal cord tensor), which is innervated by the external branch of the superior laryngeal nerve. All vocal cord abductors are controlled by the recurrent laryngeal nerve.

Airway assessment

- Complete airway assessment includes taking a history and a physical examination, noting any findings indicative of possible difficulty with mask ventilation, endotracheal intubation, or both.
- While airway management in the ICU can often be urgent or even emergent, failure to recognize predictors of a difficult airway can have potentially dire consequences.
- The most likely *predictor of airway difficulty* is a history of previous difficulty. Other 'red flags' include a history of head and/or neck radiation, airway or cervical spine surgeries, obstructive sleep apnea, presence of a mediastinal mass, or certain chromosomal abnormalities or inherited metabolic disorders.
- Time of last oral intake should be determined, if at all possible, as clear liquids within 2 hours or solid meals within 8 hours put the patient at higher risk for aspiration. Other risk factors for aspiration include gastroesophageal reflux disease (GERD), hiatal hernia, pregnancy, diabetes (gastroparesis), and morbid obesity.
- Physical examination should include assessment of the oral cavity as well as external characteristics of the head and neck, again noting potential difficulties with mask ventilation and/or intubation (Table 1.1).
- Mouth opening, presence of facial hair, and presence or absence of teeth/dentures should be assessed. Any loose teeth should be noted and dentures should be removed to avoid dislodgment and potential aspiration.
- The *Mallampati classification* describes the size of the tongue in relation to the oral cavity, which is a clinical sign developed to aid in the prediction of endotracheal intubation difficulty. The test is traditionally performed on a seated patient with the head in a neutral position, mouth opened, with the tongue protruding with no phonation. Scores are assigned based on the visibility of the oropharyngeal structures. A Mallampati class I score is indicative of relatively easy endotracheal intubation while a score of IV suggests the possibility of difficult intubation when taking other clinical signs into account (Figure 1.1).
- Examination of the neck should note any masses or goiters as well as tracheal deviation from the midline. One should note neck circumference, the ability to flex and extend the neck, as well as thyromental distance.

Table 1.1 Predictors of difficulties with mask ventilation and/or intubation.

Predictors of difficult mask ventilation	Predictors of difficult laryngoscopy
Edentulous	Overbite
Age 55 years or older	Small mouth opening <3 cm
Male patient	Mallampati class III or IV
Presence of facial hair	Thyromental distance <3 fingerbreadths
Obesity	Neck circumference >43 cm (17 inches)
Obstructive sleep apnea	Limited cervical mobility

Equipment

- Proper preparation is essential for all airway management situations.
- Essential equipment includes oxygen source (wall or tank), suction, bag-mask ventilation circuit, direct and/or video laryngoscopes, endotracheal tubes of several sizes, supraglottic airway device, blood pressure/ECG/pulse oximetry, and CO_2 detection device.
- Supraglottic airway devices include the laryngeal mask airway (LMA) which is inserted into the patient's mouth and sits above the glottis. As these devices do not protect against aspiration of gastric contents, in the ICU they are generally limited to rescue devices in situations where mask ventilation and endotracheal intubation are difficult.
- While numerous types of direct laryngoscopes are available, the two most common are the Macintosh blade (MAC) and the Miller blade. Both come in multiple sizes, but typically a MAC 3 or Miller 2 are suitable for a standard-sized adult.
- In recent years, *video laryngoscopes*, a form of indirect laryngoscopy, have become readily available in most institutions. Video laryngoscopes differ from one another in the shape of the blade, proper position when inserted into the mouth, location of the video source, and reusable/disposable parts. Glidescope® has its own (non-disposable) stylet which accompanies the unique shape of its blade. One potential problem with video laryngoscopy is that, while it may provide a clear view of the glottic opening, one still may have difficulty maneuvering an endotracheal tube into proper position.
- Endotracheal tubes (ETTs) are also available in various materials and sizes. Most commonly used in the ICU are ETTs made from polyvinyl chloride with a beveled tip to allow better visualization of insertion, a side hole (Murphy's eye) to prevent total occlusion in the event of a mucous plug, and an inflatable cuff. ETTs are sized according to internal diameter in millimeters and the appropriate size for adults is typically 7.0–8.0 mm. Bear in mind that if bronchoscopy is needed, ETTs smaller than 7.5 mm may be too narrow to accommodate an adult bronchoscope.

Positioning

- Proper patient positioning is of utmost importance and should be achieved prior to any airway intervention, particularly if direct laryngoscopy is to be attempted. Proper positioning can be the difference between a successful and unsuccessful laryngoscopy attempt.
- With the provider standing at the head of the bed, the patient's head should be as far towards the head of the bed as possible. The height of the bed should be to the provider's preference.
- Proper positioning creates a direct line of sight from the patient's mouth to the larynx. This is accomplished using approximately 30° of cervical flexion using pillows/blankets along with extension of the atlanto-occipital joint, the classic 'sniffing position.'
- Positioning obese patients may be particularly challenging. This can be accomplished by forming a ramp, elevating the upper back and shoulders in order to accommodate adequate cervical flexion. Confirming horizontal alignment of the external auditory meatus with the sternal notch can be a useful guide.

Preoxygenation

- Adequate preoxygenation should be provided in all but the most emergent situations.
- The aim is to replace nitrogen in the lungs with oxygen. This increases the length of time before desaturation when the patient is apneic ('apnea time'), providing a margin of safety in case ventilation and intubation become difficult.
- Preoxygenation can be performed using a facemask, continuous or bilevel positive airway pressure, or a high flow nasal cannula (HFNC) providing 100% oxygen at flows of at least 10 L/min. It typically requires approximately 3 minutes of normal tidal volume breathing to achieve an end-tidal oxygen concentration of approximately 90%.

- Given normal functional residual capacity (FRC) of about 2 L, and an oxygen consumption rate of about 200–250 mL/min, a properly preoxygenated adult should have an apnea time of about 5–8 minutes before significant desaturation. Reductions in apnea time should be expected in conditions in which FRC is decreased (i.e. obesity, pregnancy, tense ascites) or conditions of increased oxygen consumption (i.e. sepsis, pregnancy, hyperthyroidism).

Bag and mask ventilation

- *The ability to ventilate a patient using a bag and mask is by far the most important skill for any airway provider to master*. The inability to intubate the trachea is not fatal if mask ventilation is possible, making it a vital component of the ASA difficult airway algorithm.
- Relative contraindications to mask ventilation are full stomach/regurgitation risk, severe facial trauma, and unstable cervical spine fractures.
- Mask ventilation is performed with the provider holding the mask in his or her left hand with the mask over the patient's nose and mouth with the third, fourth, and fifth digits holding the mandible and lifting the face into the mask while the thumb and index finger form a 'C' shape around the collar aspect of the mask near the connection to the circuit. As the bag is squeezed one should note chest rise and condensation in the mask, and should hear no air escape which would indicate a leak due to an inadequate seal. Care should be used not to compress the submandibular tissue as this can collapse the airway and make ventilation more difficult.
- If mask ventilation proves difficult, one can employ a two-handed technique in which one provider holds the mask in both hands with their thumbs on top of the mask and remaining digits on the mandible lifting the face into the mask while an assistant squeezes the bag. Oral and nasal airways can also be useful as they pull the tongue and epiglottis away from the posterior wall of the pharynx, allowing more airflow.

Laryngoscopy and confirmation of placement

- After ensuring proper preparation, equipment set-up, functioning monitors, positioning and preoxygenation, the patient is typically administered an apnea-inducing medication as well as a paralytic agent, both of which are chosen based on patient conditions as well as the clinical situation. It should also be noted that in certain conditions such as cardiac arrest, induction agents may not be necessary.
- When the patient is deemed appropriately anesthetized, the laryngoscope is held in the provider's left hand while the right hand opens the patient's mouth using his or her thumb and index finger in a scissoring motion. The laryngoscope is then inserted into the mouth using care not to damage the patient's lips or teeth. In the case of the curved MAC blade, the tongue is swept to the left and the tip of the blade placed in the vallecula just anterior to the epiglottis, while the straight Miller blade is inserted in midline position beneath the epiglottis. The handle of the laryngoscope is lifted upwards and anteriorly, exposing the vocal cords. The handle should never be tilted backwards as this can result in dental damage. The ETT is then inserted through the vocal cords under direct visualization. After ETT insertion, the stylet (if used) is removed as is the laryngoscope. The pilot balloon is then inflated with air using a 10 mL syringe to no more than 30 mmHg of pressure.
- To confirm tracheal placement, the ETT is connected to a bag ventilation circuit and ventilated, observing bilateral chest rise, condensation in the ETT, and, most importantly, continuous end-tidal CO_2 via capnography – considered the gold standard. If continuous end-tidal CO_2 is not detected, esophageal intubation should be suspected and laryngoscopy should be reattempted.
- The distal tip of the ETT should lie beyond the vocal cords but above the carina, avoiding mainstem intubation. In adults this typically correlates to 21–23 cm at the patient's lip. A CXR should be ordered immediately after placement to confirm proper position.

- Video 1.1 demonstrates a successful endotracheal intubation of a morbidly obese patient. Note the ready availability of all necessary equipment including suction, laryngoscope, ETT, and oral airway. Also, note the proper patient positioning, including approximately 35° cervical flexion aided by the use of multiple blankets to ramp the shoulders as well as slight head extension. This combination allows for a nearly straight line of sight from the open mouth to the trachea. A MAC blade is used in the left hand and it sweeps the tongue to the side after the right hand scissors the mouth open. The blade is placed in the vallecula. Force is applied in a 45° direction to visualize the glottis opening, not rocked back against the upper incisors. The ETT is directly visualized as it passes between the vocal cords. The laryngoscope is then removed, and the ETT cuff is inflated with no more than 10 mL of air. While bilateral breath sounds and presence of fog in the ETT should indicate proper placement, the gold standard for proper placement is continuous end-tidal CO_2 waveform capnography.

Rapid sequence induction

- This is a specialized method of induction used when the risk of pulmonary aspiration is particularly high.
- The goal is to achieve optimal intubating conditions in the fastest time possible.
- After preoxygenation, cricoid pressure is held by an assistant while induction agents (see Chapter 2 for agents and dosages) are given followed by 1.5 mg/kg of succinylcholine or 1 mg/kg of rocuronium, and laryngoscopy is attempted without mask ventilation. Cricoid pressure is maintained until confirmation of tracheal intubation is observed.

Difficult airway

- Most difficult airways can be anticipated, and care should always be taken to recognize them with proper assessment, as unanticipated airway difficulties subject the patient to potential hypoxia, cardiovascular collapse, and neurologic damage.
- A distinction should be made as to whether the potential difficulty lies in the ability to mask ventilate, to intubate, or both.
- A good rule of thumb is to never intentionally make a patient apneic unless one is certain that ventilation will be possible.
- Proper planning and set-up, availability of equipment, positioning, and adequate preoxygenation become even more important when airway difficulty is suspected.
- In the setting of an anticipated difficult airway, additional tools such as video laryngoscopes, fiberoptic bronchoscopes as well as additional providers with the ability to provide surgical airway access should be immediately available prior to induction.
- If intubation and mask ventilation are predicted to be difficult, airway topicalization with local anesthetic and fiberoptic intubation while awake with minimal sedation is the gold standard. This should be performed with an open emergency tracheostomy set nearby as well as a provider capable of performing a surgical airway procedure. One may also attempt an 'awake look' by titrating small doses of a non-apnea-inducing hypnotic-like ketamine until a brief exam under video or direct laryngoscopy is tolerated. If this view is acceptable, one can then induce as usual and intubate the patient with the particular device.
- In the undesirable scenario where intubation is found to be difficult after induction (unanticipated difficult intubation), an attempt should be made to mask ventilate the patient and assistance should be called. If mask ventilation is easy, one can then attempt another method of intubation while confirming proper positioning and bed height. If mask ventilation is difficult, one should attempt the two-handed mask ventilation technique or placement of an oral airway. If still difficult, supraglottic airway placement such as an LMA should be considered. If ventilation remains poor, emergency invasive airway placement is likely required.

Cervical spine disease

- Cervical spine injury, whether due to trauma, previous cervical fusion resulting in limited mobility, or inflammation from rheumatoid arthritis can present challenges for airway management. The presence of a cervical collar can also make airway management difficult. Evaluation of cervical flexion and extension is prudent, and, in the case of trauma, discussions with spine surgeons regarding cervical spine stability should take place.
- In the setting of an unstable cervical spine injury, intubation with a fiberoptic bronchoscope should take place. Alternatively, direct laryngoscopy while an assistant performs inline stabilization (holding the head firmly with both hands so as to not allow unintentional cervical flexion or extension by the laryngoscopist) may be attempted.

Extubation

- While the decision to extubate is partly driven by objective data, it also relies upon clinical judgment.
- Patients should have stable vital signs, an SpO_2 of at least 90% or an FiO_2 of 40% or less, $PaCO_2$ <50 mmHg unless there is known chronic CO_2 retention, adequate tidal volumes on minimal pressure support, intact airway reflexes, and baseline mental status.
- One should also consider the specific situation such as difficulty of intubation, barriers to reintubation (e.g. jaw wired shut after maxillofacial surgery, significant airway edema), fluid balance, and acid–base balance.
- If there is any question of airway patency, one may consider performing a leak test (deflating the ETT cuff and listening for air movement around the ETT and observing a decrease in tidal volume) or extubating over an ETT exchanger with a backup ETT available in case reintubation becomes necessary.
- Patients with baseline pulmonary dysfunction may benefit from being extubated to BIPAP or HFNC.

Complications of intubation

Airway trauma

- Instrumentation of the airway can cause trauma to soft tissues as well as to teeth and lips.
- Although less common with modern ETTs, overinflation of cuffs (typically greater than 30 mmHg) can cause tissue ischemia, leading to inflammation and possibly tracheal stenosis as well as vocal cord paralysis from compression of the recurrent laryngeal nerve. Vocal cord paralysis can produce hoarseness and susceptibility to aspiration.

Physiologic effects of airway instrumentation

- Hypotension is a common response to induction and should be anticipated, especially in critically ill patients.
- Hypertension and tachycardia can be seen if inadequate anesthetic is provided.
- Laryngospasm, an involuntary closure of the laryngeal muscles, is a response to airway stimulation in the setting of light anesthesia. Severe hypoxia, from the inability to mask ventilate through the closed larynx, can result. Treatment includes gentle positive pressure with a mask. If this fails, deepening the plain of anesthesia as well as giving succinylcholine will typically relax the musculature.

Aspiration

- Critically ill patients often require airway management in the undesirable setting of a full stomach, or mechanical or physiologic motility disorders, making aspiration of gastric contents a feared complication.
- If suspected, the patient should be placed in the Trendelenburg position, the pharynx and trachea (if possible) suctioned, and the airway secured with an ETT as soon as possible.

- Therapy is typically supportive and antibiotics and bronchoscopic lavage are usually not necessary unless particulate aspiration is suspected or if signs of infection occur.

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Images

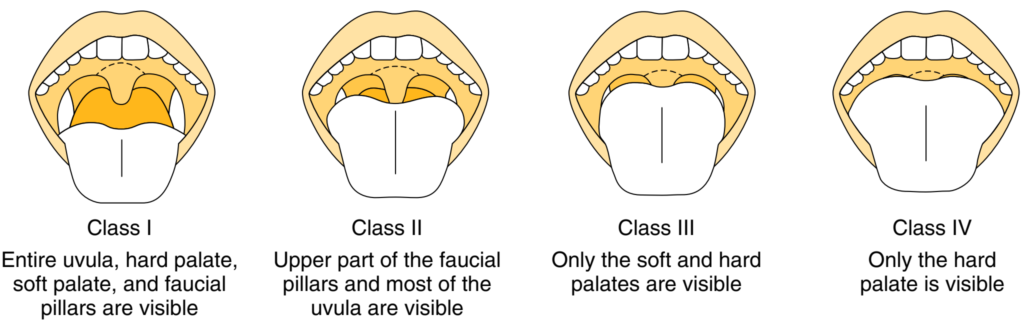

Figure 1.1 Mallampati classification.

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This includes multiple choice questions and Video 1.1.

with website

CHAPTER 2

Sedation and Analgesia

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OVERALL BOTTOM LINE

- Analgesia and sedation are primarily indicated to prevent self-harm and ensure the comfort of a patient. Examples include intubated patients who are dyssynchronous with a ventilator, those with open wounds postoperatively, and patients who are unable to have their pain controlled by less intensive measures.
- Post-traumatic stress disorder (PTSD) has been found in 20% of patients after discharge from an ICU. Appropriately targeted sedation therapy has been associated with decreased rates of PTSD.
- 'Sedation vacations' are associated with shorter length of ICU stay, fewer days on a ventilator, improved return to independent function at discharge, and trend toward lower ICU mortality.
- Pain is experienced at greater rates among the critically ill than among the wider population. Up to 70% of patients will experience moderate to severe pain during their ICU stay. Rates have been measured up to 30% while at rest and the majority will experience pain during routine cleaning and nursing interventions.
- Experiencing pain in the ICU has been associated with greater levels of chronic pain in the post ICU setting and of PTSD.
- Analgosedation, or the practice of first treating with analgesics before actively sedating the patient with hypnotics, has been linked to shorter ICU length of stay and decreased duration of mechanical ventilation.

Clinical pharmacology

- Context-sensitive half-time (CSHT) is defined as the duration of time required for plasma concentrations of a drug to decrease by 50% after discontinuing administration of the drug. 'Context' is meant to refer to the duration of time that an infusion has been running.
- The CSHT is often different from the elimination half-time and explains differences in duration of effect that exist based on how long an infusion is running versus the effect we see with a single bolus dose of a medication. As an example, if we were to believe that elimination half-time determined the duration of effect of propofol, then a single bolus should leave our patient obtunded for several hours. Instead we know that a single bolus will wear off in a few minutes due to redistribution of the medication out of the central compartment into the periphery.
- Likewise, the CSHT also explains why medications take longer for their effects to wear off after longer infusions. A simplified, if not perfectly scientific, explanation is that anesthetic drug effects wear off as medications redistribute from the central to the peripheral compartments. However, over time, the peripheral compartments can approach saturation, causing the central compartment to refill or maintain a steady state as its concentration decreases. Each drug has a different volume of periphery that it can fill

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at a different rate. Accordingly, we see that a medication like remifentanil which has virtually no CSHT will wear off in a few minutes regardless of the administration duration, while midazolam may take days after a sufficiently long infusion.

Monitoring

Sedation

- Two methods have been well validated for monitoring sedation levels with equivalent results:
  - The Richmond Agitation-Sedation Scale (Table 2.1) extends from –5 (unarousable) to +4 (combative) with zero representing a calm and alert patient. A typical goal is a light sedation of –1 to –2.
  - The Riker Sedation-Agitation Scale (Table 2.2), extends from 1 (unarousable) to 7 (dangerous agitation), with 4 representing the calm and alert patient. A typical goal is a light sedation of 3.
- Objective monitoring modalities such as EEG, bispectral index, or patient state index are not recommended by the Society of Critical Care Medicine guidelines as a regular monitoring tool. However, if the patient is paralyzed (through neuromuscular blockers or clinical condition), then use of an objective monitoring device is suggested.

Table 2.1 Richmond Agitation-Sedation Scale.

Score	Term	Description
4	Combative	Overtly combative or violent; immediate danger to staff
3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff
2	Agitated	Frequent non-purposeful movement or patient–ventilator dyssynchrony
1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
–2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
–3	Moderate sedation	Any movement (but no eye contact) to voice
–4	Deep sedation	No response to voice, but any movement to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

Table 2.2 Riker Sedation-Agitation Scale.

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, striking staff
6	Very agitated	Does not calm down despite verbal instructions, requires physical restraints
5	Agitated	Anxious or mildly agitated, calms with verbal instructions
4	Calm and cooperative	Arouses easily and follows commands
3	Sedated	Does arouse to verbal or physical stimulus, able to follow simple commands
2	Very sedated	Does not follow commands but arouses to physical stimulation
1	Unarousable	Little or no response to noxious stimuli

Pain

- Use of a validated pain scale is recommended for identifying treatment needs. Both verbal and non-verbal scales should be used based on the patient's condition.
- A *numeric ranking scale* is a subjective method of ranking pain. A typical method is the *visual analog scale* which uses a line 10 cm long with every centimeter marked as a number. The patient is asked to rank their pain along this scale, with 10 being the worst possible pain. For patients who are cognitively unable to make this association, the *faces pain scale* is an option with a series of six faces with differing expressions of distress shown. The patient is asked to point to the face that most approximates their current state.
- An *objective pain scale* can also be used as many patients are unable to actively participate in their own pain assessment due to intubation and sedation or cognitive problems. The two best validated methods are the *behavioral pain scale* (BPS) and the *critical care pain observation tool* (CPOT). Additionally, the CPOT has recently been shown to be valid in patients with traumatic brain injury.
- The BPS is comprised of three domains: facial expression, upper limb movement, and compliance with ventilation, each scored from 1 through 4. A total score of 5 or less is considered acceptable pain control.
- The CPOT is comprised of four domains: facial expression, body movements, compliance with the ventilator or vocalization, and muscle tension, each scored from 0 to 2 with a total possible score of 8.

Medications for sedation and analgesia

Recommended doses are from the Society of Critical Care Medicine (SCCM) 2013 Pain, Agitation, and Delirium Guidelines.

Opioids

- Considered the first line analgesic by the SCCM guidelines for ICU patients.
- As a class, they have some sedative properties when given in high enough doses, but have no amnestic effects.
- Side effects are reasonably universal and include respiratory depression, hypotension, itching, nausea and vomiting, miosis, and decreased gastric motility.
- Choice of opioid and dosage must be tailored to the individual patient. For example, a 24-year-old patient in a trauma ICU who was actively taking suboxone at the time of admission may require an order of magnitude more opioid for the first 24 hours than a 72-year-old patient with renal failure.

Fentanyl

- Pharmacology:
  - Synthetic opioid with no active metabolites.
  - Broken down through the CYP3A4 pathway, with a potential for prolonged effect with certain chemotherapy agents.
  - Highly lipid soluble.
  - Onset of action 1–2 minutes, duration of effect ~40 minutes.
  - Elimination half-life 2–4 hours.
  - CSHT is 200 minutes after a 6 hour infusion, and 300 minutes or greater after a 12 hour infusion (this can increase unpredictably in multiorgan failure).
- Drug-specific side effects:
  - Chest wall rigidity: a very uncommon side effect of synthetic opioids that can be complicated by glottic closure and trismus. Appears somewhat related to dosage, rapidity of administration, extremes of age, presence of critical illness, and use of antidepressant medications. Can render a patient unable to ventilate. Requires immediate reversal with naloxone and preparations for emergent intubation with a neuromuscular blocker. If no further complications are noted (e.g. negative pulmonary pressure edema due to closed glottis), extubation can be attempted within minutes of cessation of rigidity and

neuromuscular blockade. This is not an allergic reaction and does not preclude the patient from receiving this analgesic agent in the future.

- Recommended doses:
  - Bolus: 0.35–0.5 μg/kg IV every 0.5–1 hour.
  - Infusion: 0.7–10 μg/kg/h.
  - PCA: bolus 15–75 μg, lockout interval 3–10 minutes.

Hydromorphone

- Pharmacology:
  - Semisynthetic opioid.
  - Hepatic metabolism, renal elimination.
  - No active metabolites.
  - Onset of action 5–15 minutes, duration of effect 3–4 hours.
  - Elimination half-life 2–3 hours.
- Drug-specific side effects:
  - Some histamine release with administration.
- Recommended doses:
  - Bolus: 0.2–0.6 mg IV every 1–2 hours.
  - Infusion: 0.5–3 mg/h.
  - PCA: bolus 0.1–0.5 mg, lockout interval 5–15 minutes.

Morphine

- Pharmacology:
  - Poorly lipid soluble.
  - Hepatic metabolism with active metabolite morphine-6-glucuronide.
  - Renally eliminated.
  - Onset of action 5–10 minutes, duration of effect 4–5 hours.
  - Elimination half-life 3–4 hours.
- Drug-specific side effects:
  - Accumulation can occur in renal failure.
  - Can cause clinically significant histamine release.
- Recommended doses:
  - Bolus: 2–4 mg IV every 1–2 hours.
  - Infusion: 2–30 mg/h.
  - PCA: bolus 0.5–3 mg, lockout interval 10–20 minutes.

Methadone

- Pharmacology:
  - Synthetic opioid with antagonism of NMDA receptors along with usual agonism of opioid receptors.
  - Hepatic metabolism and renal elimination.
  - No active metabolites.
  - Onset of action 10–20 minutes, duration of effect 6–8 hours.
  - Elimination half-life 15–60 hours.
- Drug-specific side effects:
  - QTc prolongation: ECG monitoring is recommended while using this drug.
- Recommended doses:
  - Bolus: 10–40 mg every 6–12 hours.
  - Infusion: not recommended.

Benzodiazepines

- Associated with increased rates of delirium and PTSD.
- Anxiolytic, amnestic, and anticonvulsant.
- GABA agonist.
- No analgesic properties.
- Synergistic respiratory depression with opioids.
- Can cause hypotension.
- Hepatic metabolism and renal elimination.

Midazolam

- Pharmacology:
  - High lipid solubility.
  - Active metabolites.
  - Only benzodiazepine formulation without propylene glycol as solvent.
  - Metabolized by several cytochrome P450 enzymes.
  - Onset of action 2–5 minutes, duration of effect 1–2 hours.
  - Elimination half-life 3–11 hours, significant CSHT.
  - Cessation of effect is due to redistribution.
- Drug-specific side effects:
  - Renal elimination of active metabolites.
- Recommended doses:
  - Bolus: 0.01–0.05 mg/kg.
  - Infusion: 0.02–0.1 mg/kg/h.

Lorazepam

- Pharmacology:
  - No active metabolites.
  - Onset of action 15–20 minutes, duration of effect 1–2 hours.
  - Elimination half-life 3–11 hours.
- Drug-specific side effects:
  - Typical solutions contain propylene glycol that can cause metabolic acidosis and acute kidney injury when run as an infusion. A serum osmolar gap greater than 10–12 mOsm/L suggests propylene glycol toxicity.
- Recommended doses:
  - Bolus: 0.02–0.04 mg/kg (maximum dose 2 mg) every 2–6 hours as required.
  - Infusion (generally not recommended): 0.01–0.1 mg/kg/h (maximum dose <10 mg/h).

Diazepam

- Pharmacology:
  - Active metabolites.
  - Onset of action 2–5 minutes IV, peak effect 1-2 hours, duration of effect variable but typically 4–6 hours.
  - Can be given per rectum for seizure treatment if no intravenous access.
  - Elimination half-life 20+ hours due to active metabolites.
- Drug-specific side effects:
  - Respiratory depression.
  - Phlebitis.
  - Uses propylene glycol as solvent.
  - Accumulation of metabolites in renal failure.
- Recommended doses:
  - Bolus: 5–10 mg IV.

- PRN dosing: 0.03–0.1 mg/kg every 0.5–6 hours.
- Rectal dose for seizures: 0.2 mg/kg seizures, every 4–12 hours as required, status epilepticus 0.5 mg/kg bolus and 0.25 mg/kg every 10 minutes as required.

Other sedatives

Propofol

- Pharmacology:
  - Predominantly agonist at GABA receptor.
  - Hypnotic, antiemetic, and anticonvulsant.
  - No analgesic properties.
  - 98% protein bound.
  - No active metabolites.
  - Onset of action 1–2 minutes, duration of effect 5–10 minutes.
  - Propofol is delivered in a fat emulsion that provides 1.1 kcal/mL. This should be considered when adjusting enteral and parenteral nutritional requirements.
- Side effects:
  - Vasodilation and hypotension.
  - Myocardial depression.
  - Respiratory depression.
  - Pancreatitis.
  - Propofol infusion syndrome:
    - A potentially lethal syndrome marked by metabolic acidosis, hypertriglyceridemia, and hypotension refractory to vasopressors.
    - Believed due to mitochondrial dysfunction.
    - Treatment is cessation of infusion and supportive.
    - Associated with prolonged infusions of greater than 70 μg/kg/min.
    - Incidence of propofol infusion syndrome 1%, mortality 33%.
- Recommended doses:
  - Bolus: 0.1–0.3 mg/kg slowly.
  - Infusion: 5–50 μg/kg/min.

Dexmedetomidine

- Pharmacology:
  - Alpha-2 receptor agonist.
  - Minimal respiratory depression.
  - Hypnotic and analgesic properties.
  - No active metabolites.
  - Onset of action after loading dose 5–10 minutes.
- Side effects:
  - Hypertension: often associated with loading doses.
  - Hypotension: often associated with loading doses.
  - Bradycardia.
- Recommended doses:
  - Loading dose: 1 μg/kg over 10 minutes.
  - Infusion: FDA approved for 0.2–0.7 μg/kg/h for up to 24 hours; reports have shown safety with maximum infusion 1.5 μg/kg/h for up to 1 month.
- Miscellaneous:
  - No proven benefit to delirium.

Ketamine

- Pharmacology:
  - NMDA antagonist.
  - Hypnotic and analgesic.
  - Active metabolite norketamine.
  - There should be no expectation of decreased opioid use or rates of delirium after a single intraoperative dose of ketamine.
  - Onset of action 30–40 seconds.
  - Elimination half-life 2–3 hours.
- Side effects:
  - Increased salivation.
  - Potential for increased intracranial pressure (ICP)
  - Potential for sympathetic discharge.
  - Hallucinations: can be attenuated by simultaneous administration of benzodiazepine.
  - Negative inotropy: may be harmful in heart failure patients; further research is warranted.
- Recommended doses:
  - Bolus: 0.1–0.5 mg/kg IV.
  - Infusion: 0.05–0.4 mg/kg/h.

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CHAPTER 3

Vascular Access

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OVERALL BOTTOM LINE

- Providers need to optimize central venous catheter and arterial catheter insertion in critically ill patients.
- Strict sterile technique during insertion is crucial for minimizing infection, the most serious and frequent complication associated with line placement.
- In general, central venous and arterial lines should be removed as soon as possible to minimize the risk of infection.

Central venous access

Indications

- Difficult venous access, frequent blood sampling.
- Rapid administration of fluids and blood products (resuscitation).
- Administration of fluids and medication caustic to small veins (e.g. vasopressors, chemotherapy, total parenteral nutrition).
- Renal replacement therapy, plasmapheresis.
- Transvenous pacemaker, pulmonary artery catheter.

Venous access sites

- Internal jugular (IJ), subclavian medial (SM) or lateral (SL), and femoral (F) veins.

Catheter types (Figure 3.1)

- Multilumen or single lumen (central venous access catheters).
- Dialysis (large bore, double, or multilumen catheters).
- Introducer (large bore for rapid resuscitation access, temporary pacemaker, or pulmonary artery catheter insertion).

Procedure

- Prior to procedure, ensure that the patient's name, procedure, and site of insertion are confirmed with the patient's nurse.
- Pre-procedure US: the vein is visualized under US when using the IJ, SL, or F veins for access. (Note: the SM vein approach places the needle tip under the clavicle, hence it is not possible to visualize cannulation of the subclavian vein under US when using this approach.) Scan above, at, and below site of planned insertion (or lateral to medial with SL approach) with compression to check for thrombosis (Figure 3.2) or

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stenosis. Video 3.1 demonstrates the appearance of the vessels when performing the SL approach. On the viewer's left, cephalad (towards the head, i.e. closer to the clavicle) is the subclavian artery (SA); to the viewer's right, caudad (towards the feet, i.e. closer to the lung) is the subclavian vein (SV) (since the vessel has not yet passed the first rib, technically speaking it may be called the axillary vein). Note that the SV is compressible and non-pulsating. Also note the twinkling horizontal line about 0.5 cm below the SV coming in from the right side with respiration: this is the pleural line.

- For any neck line insertion (IJ or SM/SL sites) pre-scan (US) the pleura on the side of planned insertion for the presence and degree of lung sliding. (See Chapter 4, Videos 4.1 and Video 4.2.) This can improve the accuracy of post-procedure US to assess for pneumothorax.
- Optimize site of insertion by selecting a plane where the artery is not directly beneath the vein (IJ insertion) or directly overlying the vein (F insertion) if possible. For IJ lines, turning the patient's head toward the side of insertion may move the IJ to a more lateral position relative to the carotid artery. For F lines, moving the US superiorly toward the inguinal ligament will locate the vein medial to the artery. Moving the US down the leg (away from the inguinal ligament in the direction of the knee) will locate a position where the artery is overlying the vein, making access more difficult. Also, flexion of the lower extremity at the knee with lateral rotation may also help to move the femoral vein more medially from under the femoral artery. US will demonstrate whether this maneuver is effective or not.
- Select the depth on the US machine (Figure 3.3) where both vein and artery can be easily visualized at their largest on the screen, i.e. minimum depth needed (a rough guide is approximately 2–3 cm for IJ, 4–5 cm for SL [for SL this includes visualization of the pleural line], and 3–5 cm for F). (Note: this requires a transverse orientation of the US probe. A longitudinal orientation will only show the vein, not the artery, unless the artery is directly beneath the vein. The transverse approach is preferred to prevent inadvertent arterial puncture, especially in less experienced or in-training practitioners.)
- Clean site of insertion plus a diameter of approximately 15 cm with chlorhexidine gluconate and isopropyl alcohol (e.g. Chloroprep).
- Wash hands and put on cap, mask, sterile gown, and sterile gloves.
- Prepare sterile field: drape patient with sterile sheets and drapes so that only prepped area is exposed.
- Place sterile US gel into sterile US probe cover, then insert US into sterile covering; fasten covering with rubber bands.
- Place sterile US gel onto insertion site.
- Draw up 5–10 mL 1% lidocaine and label syringe.
- Flush all ports of the catheter with sterile saline; for triple lumen catheters, clamp blue and white ports, but leave brown port unclamped; for dialysis catheters, clamp red port, but leave blue port unclamped (guidewire exits this port).
- Remove and gently but firmly replace the introducer (i.e. insertion) needle onto the syringe ensuring the needle is not jammed onto the syringe.
- Remove cap off guidewire (GW) and retract GW into plastic sheath until 2 mm is exposed.
- Place gauze on sterile field near insertion site.
- Draw sterile saline into syringe in preparation to flush all ports post-insertion.
- Set up tools on sterile table in the order in which they will be used: lidocaine, insertion needle and syringe, GW, skin dilator, scalpel, catheter, needle holder, suture.
- Hold US probe in the non-dominant hand, select insertion site, inject 3–10 mL lidocaine with dominant hand, and place lidocaine syringe into sharps sponge.
- Hold US with non-dominant hand; hold insertion needle and syringe with dominant hand (Video 3.2).
- As soon as insertion needle pierces the skin, introduce negative pressure by pulling the plunger on the syringe.
- Slowly advance syringe at a 70–80° angle under US guidance (Figure 3.4).
- As soon as blood is aspirated into the syringe and introducer needle tip is visualized inside the vein near the center (Video 3.3: see at 30–31 seconds), place US down and stabilize the introducer needle with the non-dominant hand. Twist syringe off with dominant hand.

- Advance GW into insertion needle until 20 cm mark is just before the entry point into the introducer needle; the 20 cm mark is visualized as two parallel gray lines on the GW. Look at the ECG monitor; if new atrial or ventricular ectopy or arrhythmias are present, immediately withdraw the GW and then reinsert to a shallower depth, e.g. 15 cm.
  - If any difficulty is encountered during GW insertion (wire not advancing, e.g. bouncing back), withdraw GW, reattach introducer syringe and apply negative pressure while visualizing the vein under US. Never force GW into vein as this can cause damage to vessel walls, vein perforation, and artery cannulation. Excessive force placed on GW will result in a bent wire.
  - If insertion needle is noted to be centrally located inside vein (e.g. not buried into the posterior wall) and GW cannot be advanced, turn insertion needle 90° and attempt to advance GW.
  - If friction or bounce is still encountered after several attempts, remove insertion needle and attempt procedure again at a different site.
- Remove insertion needle and place in sharps sponge.
- Visualize GW in vein and *not* in artery with US (both criteria must be met) (Figure 3.5).
- Load skin dilator onto GW, leaving a gap of 2 cm from the skin.
- Using the scalpel, make a small skin nick at point of insertion. Withdraw scalpel into protective sheath before placing on sterile table. Note: in cases of thin skin tissue, it may be possible to advance the dilator without making a scalpel nick. This can help to reduce post-procedure insertion site bleeding and should be considered especially in coagulopathic patients or patients who will be started on therapeutic anticoagulation post-procedure.
- Advance skin dilator approximately 3–4 cm, then remove dilator. Use the other hand to hold point pressure at insertion site to prevent bleeding.
- Advance catheter over the GW, ensuring that contact with the GW is maintained at all times (i.e. there must always be one hand holding the GW when placing the GW and when placing the catheter over the GW).
- As the catheter approaches the skin, pull GW out until it exits (brown port of triple lumen catheter or blue port of dialysis catheter). Hold this end of the GW with one hand as the other hand advances the catheter into the vessel.
- Remove GW. After GW is completely removed, verbalize to nurse 'wire out.'
- Apply gentle negative pressure until blood is seen in the port tubing, then flush port with sterile saline. Ensure port tubing is free from blood, then clamp. Repeat for all ports. Apply caps onto all ports.
- Instill 1 mL of lidocaine near each suture site.
- Suture catheter to skin, ensuring sutures are snug, but not overly tight or loose.
- Clean insertion site with chlorhexidine gluconate and isopropyl alcohol and allow to dry (1–2 minutes).
- Apply dressing, e.g. Biopatch (hydrophilic polyurethane absorptive foam with chlorhexidine gluconate) then Tegaderm (transparent film dressing), or Tegaderm with impregnated chlorhexidine alone (Biopatch not needed).
- Jugular and subclavian catheters usually require CXR to confirm position prior to use unless in an emergency; femoral catheters can be immediately used.
- If there are signs or symptoms suggestive of pneumothorax at any point in the procedure after vein cannulation, perform pleural US on the side of the procedure. Lung sliding rules out pneumothorax. (See Chapter 4, Videos 4.1 and 4.2.)

Management of complications

- Thrombosis: catheter removal, evaluate need for anticoagulation.
- Bleeding at insertion site: point pressure (hydrophilic polymer and potassium ferrate powder (e.g. StatSeal) to stop bleeding), suturing.
- Inadvertent arterial insertion: call vascular surgery for removal; do not attempt to remove the catheter yourself.

Follow-up

- Catheter site should be examined daily to ensure that insertion site is clean, dry, and without erythema or discharge.
- Dressing should be changed when soiled and at least once weekly.
- Catheters should be left in place no longer than necessary and should be removed as soon as indications resolve.

Arterial access

Indications

- Continuous blood pressure monitoring (e.g. on vasoactive therapy, shock).
- Frequent arterial blood sampling (e.g. respiratory failure, shock).

Arterial sites

- Radial, axillary, femoral.

Catheter types

- Radial, axillary, femoral (Figure 3.6).
- Angiocatheter, assembly needle (angiocath and GW incorporated into a single unit), separate GW and needle (Figure 3.7).

Procedure

- Prior to procedure, perform time out where the patient's name, procedure, and site of insertion are confirmed with the patient's nurse.
- Pre-procedure US: artery (radial, axillary, femoral) is visualized under US at and proximal to insertion site for stenosis.
- Optimize site of insertion. For radial, supinate hand and tape hand down. For axillary, place a soft wrist restraint to help pull arm above patient's head.
- Select the depth on the US machine where artery can be easily visualized, i.e. minimum depth needed (a rough guide is approximately 2 cm for radial, 2–3 cm for axillary, and 4–5 cm for femoral). (Note: this requires a transverse orientation of the US probe.)
- Clean site of insertion plus a diameter of approximately 15 cm with chlorhexidine gluconate and isopropyl alcohol (Chloroprep).
- Wash hands and put on cap, mask, sterile gown, and sterile gloves.
- Prepare sterile field: drape patient with sterile sheets and drapes so that only prepped area is exposed.
- Place sterile US gel into sterile US probe cover, then insert US into sterile covering; fasten covering with rubber bands.
- Place sterile US gel onto insertion site.
- Draw up 5–10 mL 1% lidocaine and label syringe.
- Remove and gently but firmly twist the introducer (i.e. insertion) needle onto syringe.
- Remove GW from paper covering and retract GW into plastic sheath until 2 mm is exposed.
- Place gauze on sterile field near insertion site.
- Set up tools on sterile table in the order in which they will be used: lidocaine, insertion needle and syringe, GW, catheter, needle holder, suture.
- Hold US in the non-dominant hand, select insertion site, inject 3–4 mL lidocaine with dominant hand, and place lidocaine syringe into sharps sponge.
- Hold US with non-dominant hand; hold insertion needle and syringe with dominant hand.

- As soon as insertion needle pierces the skin, introduce negative pressure by pulling the plunger on the syringe.
- Slowly advance syringe at a steep, 70–80° angle for axillary (Figure 3.8A) or femoral arterial cannulation; use a more shallow angle (e.g. 45° or less) for radial arterial cannulation (Figure 3.8B), all under US guidance.
- As soon as blood is aspirated into syringe and introducer needle tip is visualized inside the artery, near its center, place US probe down and stabilize introducer needle with non-dominant hand. Twist syringe off with dominant hand. (Optionally the needle may be inserted without an attached syringe depending on operator preference.)
- Advance half the length of GW into insertion needle:
  - If any difficulty is encountered during GW insertion (wire not advancing, e.g. bouncing back), withdraw GW, reattach introducer syringe, and apply negative pressure while visualizing artery under US. Never force GW into artery as this can cause damage to vessel walls and arterial perforation. Excessive force placed on GW will result in a bent wire.
  - If insertion needle is noted to be centrally located (e.g. not buried into the posterior wall) inside the artery and GW cannot be advanced, turn insertion needle 90° and attempt to advance GW.
  - If resistance or bounce is still encountered, remove insertion needle and place point pressure until hemostasis is confirmed; after hemostasis is achieved, procedure can be attempted again at a different site.
- Remove insertion needle and place in sharps sponge.
- Visualize GW in artery with US.
- Advance catheter over GW, ensuring that contact with the GW is maintained at all times (i.e. there must always be one hand holding the GW when placing it and when placing the catheter over the GW).
- As the catheter approaches the skin, pull GW out until it exits the arterial catheter. Hold this end of the GW with one hand as the other hand advances the catheter into the vessel.
- Remove GW and immediately cover end of catheter to prevent bleeding. After GW is completely removed, verbalize 'wire out.'
- Apply connective tubing to the arterial catheter in sterile fashion.
- Have the nurse forward flush the arterial catheter, then check for a good waveform on the monitor (Figure 3.9) before securing the catheter.
- Instill 1 mL of lidocaine at the intended suture sites.
- Suture catheter to skin: place suture through skin, then wrap suture around arterial catheter three times before tying knot. Ensure sutures are snug, but not overly tight or loose.
- Clean insertion site with chlorhexidine gluconate and isopropyl alcohol and allow to dry (1–2 minutes).
- Apply dressing, e.g. Tegaderm (transparent film dressing) or Tegaderm with impregnated chlorhexidine.
- Note: the description above describes using a free GW with a separate needle and catheter. Some kits have the GW integrated into the needle and catheter assembly (Figure 3.7B); in this case after gaining access to the artery the GW is advanced through the assembly into the artery, followed by catheter insertion over the GW and removal of the entire assembly. Alternatively, radial artery access can also be performed without a GW, using an angiocatheter over a needle assembly in a fashion similar to inserting an intravenous catheter (Figure 3.7A), advancing the catheter over the needle after cannulating the artery.

Management of complications

- Thrombosis: catheter removal, vascular surgery consultation, anticoagulation as indicated.
- Hematoma: point pressure (hydrophilic polymer and potassium ferrate powder (StatSeal) to stop bleeding), suturing, vascular surgery consultation.
- Nerve compression (e.g. axillary artery pseudo-aneurysm): catheter removal, vascular surgery/neurology consultation.

Follow-up

- Catheter site should be examined daily to ensure that insertion site is clean, dry, and without erythema or discharge.
- Dressing should be changed when soiled and at least once weekly.
- Catheters should be removed as soon as indications resolve.
- After arterial catheter removal: nurse should monitor insertion site for bleeding/hematoma for 2 hours.

Reading list

Killu K, et al. Utility of ultrasound versus landmark-guided axillary artery cannulation for hemodynamic monitoring in the intensive care unit. ICU Director 2011;May:54–9.

Saugel B, Scheeren TWLW, Teboul J-LL. Ultrasound-guided central venous catheter placement: a structured review and recommendations for clinical practice. Crit Care 2017;21(1):225.

Weiner M, Geldard P, Mittnacht A. Ultrasound-guided vascular access: a comprehensive review. J Cardiothorac Vasc Anesth 2013;27(2):345–60.

Suggested websites

http://www.carefusion.com/our-products/browse-brands/chloraprep

http://www.ethicon.com/healthcare-professionals/infection-prevention/biopatch-protective-disk-chg

http://www.3m.com/3M/en_US/company-us/all-3m-products/~/All-3M-Products/Health-Care/Medical/Tegaderm/?N=5002385+8707795+8707798+8711017+8711738+3294857497&rt=r3

Images

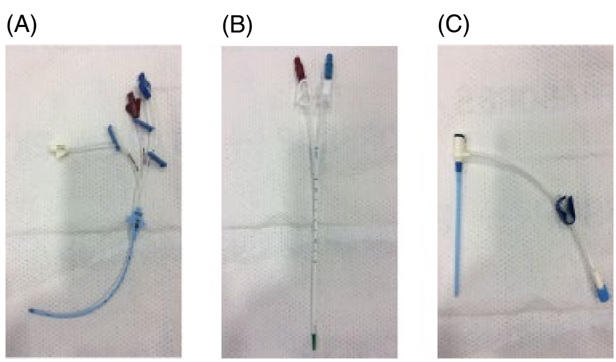

Figure 3.1 Catheter types: (A) multilumen, (B) large bore (e.g. dialysis, plasmapheresis), and (C) introducer.

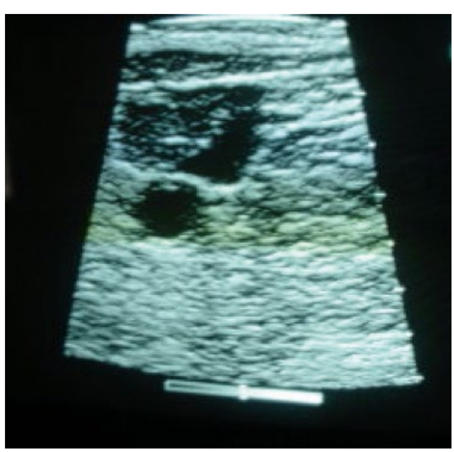

Figure 3.2 Non-occlusive thrombus in right internal jugular vein.

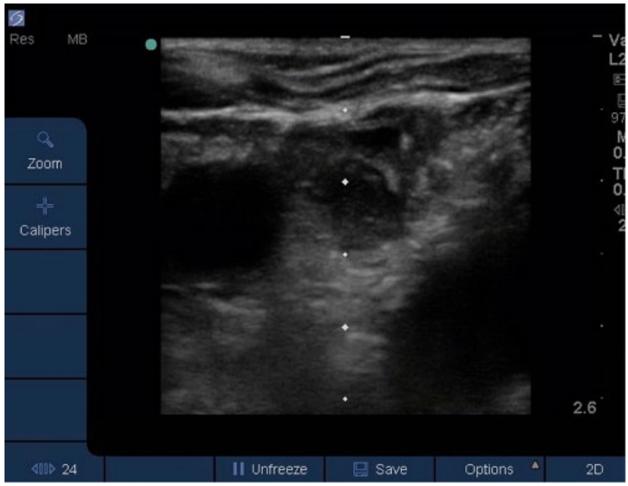

Figure 3.3 Depth scale set at 2.6 cm. Note that entry point to vessel is at 1 cm. The operator should be aware of these depths while performing the procedure.

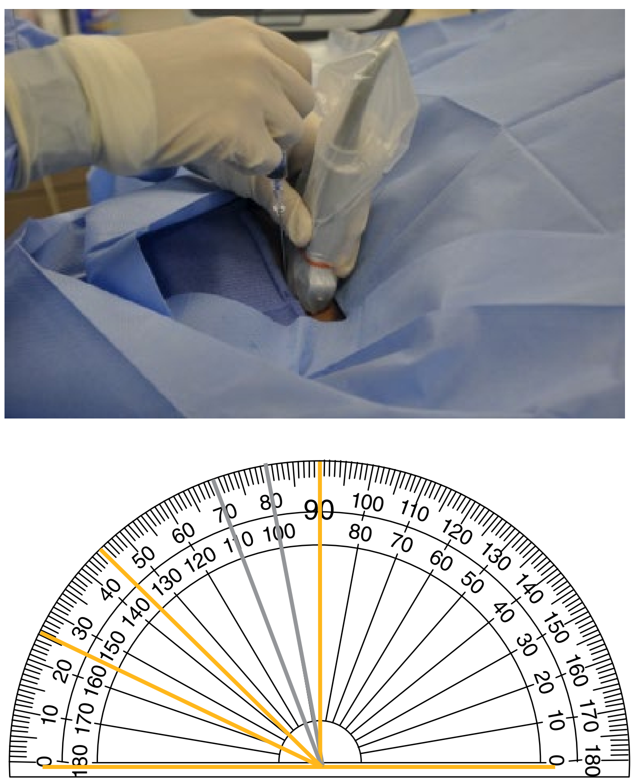

Figure 3.4 Note the angle between the needle and ultrasound probe is 70–80°. This optimizes needle tip visualization and vein penetration. This angle is suggested for central venous access of the internal jugular, lateral subclavian (or axillary), and femoral veins.

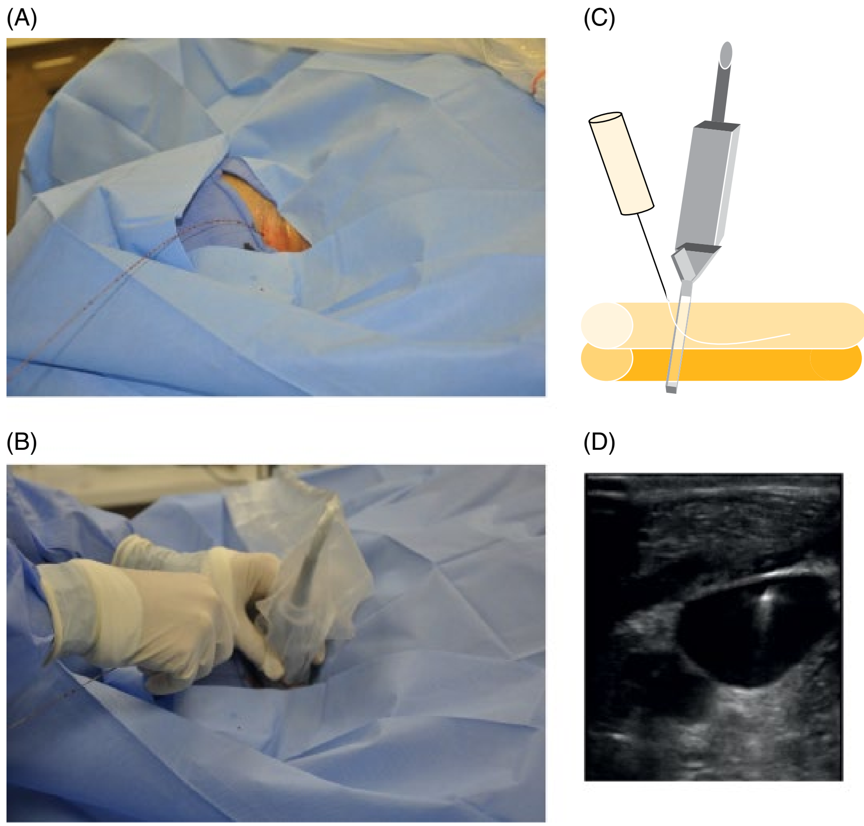

Figure 3.5 Ultrasound of the guidewire. (A) Following cannulation of the vein the guidewire is passed through the introducer needle and the needle is removed. (B) The ultrasound is again placed at the insertion site to visualize the guidewire (C) and confirm that the guidewire is in the vein and *not* in the artery (D) before dilation of the vessel is performed.

Figure 3.6 Arterial line catheter types. (A) Longer catheter (12 cm) used for axillary or femoral arterial lines. (B) Shorter catheter (4.5 cm) used for radial arterial lines.

Figure 3.7 Arterial line catheter types. (A) Angiocatheter. (B) Assembly (needle, angiocath, and guidewire incorporated into a single unit). (C, D) Guidewire and introducer needle separately.

(A)

(B)

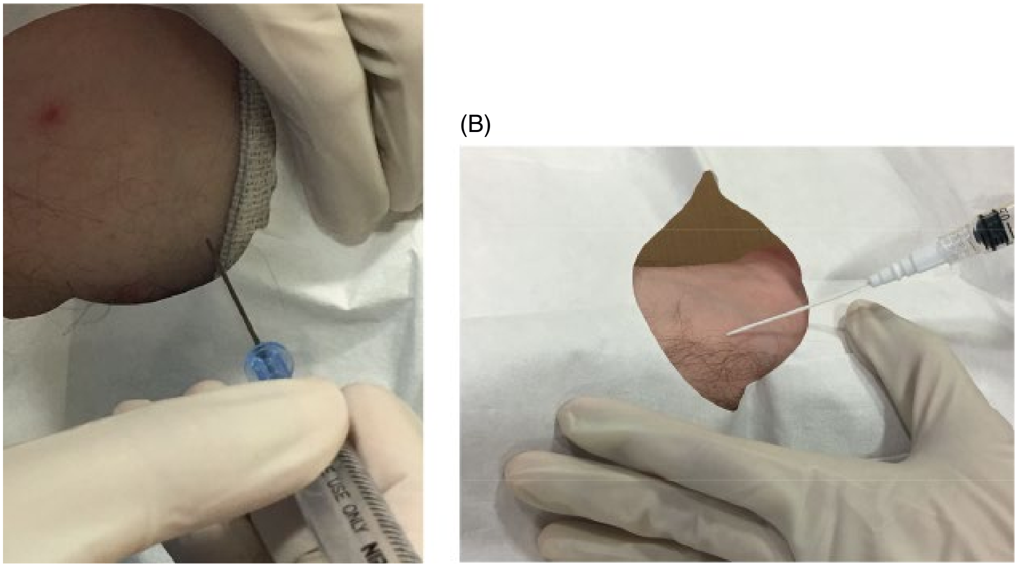

Figure 3.8 Introducer needle angles for arterial catheter insertion. (A) Axillary line cannulation with needle positioning shown at a steeper angle (70–80°). This steeper angle is used to improve visualization of the needle tip under ultrasound (not shown) in the larger axillary or femoral vessels. (B) Radial line cannulation with needle positioning shown at a more shallow angle (e.g. 45° or less) to avoid penetrating the posterior wall of this small artery.

Figure 3.9 Arterial line waveform with peak wave followed by dicrotic notch. An adequate waveform (e.g. not damped) should be confirmed *before* suturing the catheter in place.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions and Videos 3.1, 3.2 and 3.3.

CHAPTER 4

Bedside Ultrasound

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OVERALL BOTTOM LINE

- Bedside US is a safe, non-invasive diagnostic procedure that allows rapid evaluation of undifferentiated hypotension and identification of reversible causes of shock. It is also a useful tool for promptly excluding immediately life-threatening emergencies.
- The focused assessment using sonography for trauma (FAST) exam is the standard of care in the initial evaluation of trauma patients with hypotension or signs of shock. Until recently, there was no standardized sonographic approach for evaluating the critically ill medical patient.
- In 2009, the American College of Chest Physicians produced a consensus statement describing competence in critical care US. The components of critical care US the intensivist should achieve competence in for routine ICU operations include the following:
  - Critical care echocardiography.
  - Pleural ultrasonography.
  - Lung ultrasonography.
  - Abdominal ultrasonography.
  - Vascular ultrasonography: guidance of vascular access and diagnosis of venous thrombosis.

Indications

- Initial evaluation of undifferentiated hypotension and shock.
- Non-invasive monitoring of hemodynamic status and following response to therapy.
- Respiratory failure.
- Cardiac arrest.
- Vascular access.

Basic concepts

Ultrasound physics (Table 4.1)

- Sound waves: series of mechanical pressure waves that require a medium to travel through.
- US waves undergo attenuation, reflection, refraction, and scattering as they travel through tissue.
- Acoustic impedance: resistance of tissue to passage of US waves.
- Degree of reflection is determined by difference in acoustic impedance of two tissues at interface.
- US image is formed from reflected echoes.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Table 4.1 Features of ultrasound physics.

Body tissue	Acoustic impedance	Degree of reflection
Air	Very low	High
Liver, blood, kidney	'Average' soft tissue	Low
Bone	Very high	*High*

Table 4.2 Probe types.

Linear array probe	Phased array probe	Large curvilinear probe
Commonly referred to as vascular probe • High frequency (typically 5–10 MHz) • Large footprint • Excellent image resolution of superficial structures at expense of tissue penetration • Use: vascular, lung (specifically pleura)	*Commonly referred to as cardiac probe* • Small footprint; sound waves originate from single point and fan outward • Low frequency (typically 1–5 MHz) • Excellent tissue penetration at expense of image resolution • Use: cardiac, lung, abdomen	• Large footprint; sound waves originate from large area and fan outward • Low frequency (typically 2–5 MHz) • Excellent tissue penetration at expense of image resolution • Use: abdomen

Ultrasound equipment

- Transducer (probe): sends out US waves that pass through tissue; also senses sound waves reflected back to transducer.
- Structures closest to transducer are displayed at top of US screen in 'near field.'
- All probes have an 'indicator' (typically a bump or groove) on one side of the transducer that corresponds to an index marker on the US screen. Types of probes: see Figure 4.1 and Table 4.2.
- General radiology convention is to position the screen index marker on left side of screen, and 'point' the probe indicator to patient's right side or head. This means images on left side of screen correspond to structures on patient's right side or toward patient's head, respectively.
- Cardiologists use an opposite convention (discussed in more depth in Procedure section).
- It is critical to confirm your probe orientation with gel prior to any US exam or procedure. Relative to you, with the probe placed just above the intended point of contact, tapping under the right side of the probe should result in movement on the right side of the ultrasound screen. If movement occurs on the left side of the screen, rotate the probe 180°.

Basic knobology

- Depth: adjusts depth of field of view by increasing or decreasing depth of US beam. Increasing depth will visualize deeper structures and decreasing will enlarge superficial structures.
- Gain: adjusts brightness of image by changing amplification of returning echoes.
- Time-gain compensation: adjusts gain at selective depths to account for tissue attenuation; echoes returning from deeper tissues will be weaker.
- Freeze: creates 'still' or 'frozen' 2D images.
- Modes:
  - B-mode (brightness): standard scanning mode using different shades of gray to provide structural information in 2D image.
  - M-mode (motion): temporal measurement of structures moving toward or away from probe.
  - Color Doppler: distinguishes vascular from non-vascular structures and shows direction of flow.

Basic terminology

- Echogenicity: brightness (amplitude) of image.
- Hyperechoic/echogenic: structure appears brighter/whiter by generating more echoes than surrounding tissue.
- Hypoechoic: structure appears darker than surrounding tissue by generating few echoes.
- Isoechoic: same brightness as surrounding tissue.
- Anechoic: area appears black due to complete absence of echoes.

Artifacts of US imaging

- Shadowing: partial or total reflection of US waves (gallstones, ribs).
- Posterior enhancement: area behind anechoic fluid-filled structures appears brighter (bladder).
- Edge artifact: shadow formed by refraction of US wave at edge of rounded structure.
- Mirror artifact: image of structure duplicated as US wave reflects off highly reflective surface (diaphragm).
- Reverberation artifact: US wave bounces between two highly reflective surfaces (pleura).
- Ring-down artifact: appearance of needle tip as a hyperechoic structure casting a narrow shadow.

Procedure

Cardiac ultrasonography

Probe selection and orientation

- Use phased array 'cardiac' probe.
- Conventional cardiology screen/probe orientation is to position the screen index marker on the right side of the screen (reverse of general radiology convention).

Scanning technique

- There are four standard views (Figure 4.2).
- *Parasternal long axis*. Position probe just left of sternum at the third or fourth intercostal space. When using conventional cardiology orientation (marker on right side of screen), point probe indicator towards patient's right shoulder. If you prefer keeping the screen marker fixed on the left side while obtaining views consistent with conventional cardiology imaging, simply point probe in opposite direction towards patient's left hip. Otherwise, images will be reversed.
- *Parasternal short axis*. Rotate probe 90° from long axis view to obtain circular short axis view of left ventricle. For conventional cardiology orientation, this means pointing probe towards the patient's left shoulder. For general radiology orientation, point probe towards patient's right hip. Angling probe through short axis views allows visualization of different segments of the left ventricle, including apex, papillary muscles (mid-section), mitral valve (base of heart), and aortic valve (*'Mercedes Benz' sign*).
- *Apical four chamber*. Using same orientation as short axis view, slide probe leftward – lateral to nipple line (men) or inframammary crease (women) – to point of maximal impulse. Position probe so ventricular septum is in center of US screen. The left heart will be on right side of screen and vice versa.
- *Subxiphoid*. Position probe just below subxiphoid and angle cephalad toward the patient's left shoulder using the liver as an acoustic window. If using conventional cardiology orientation, point probe towards patient's left side. Otherwise, point probe towards patient's right side. Transition to evaluating the inferior vena cava (IVC) from this view.

Clinical application

- Assess for pericardial effusion or tamponade:
  - Effusion appears as anechoic area within pericardial space.
  - Large effusions tend to wrap circumferentially around heart.

- Clotted blood or exudates appear more echogenic.
- If effusion is identified, observe closely for diastolic collapse of right heart which indicates tamponade physiology.
- Determine global left ventricular (LV) function, systolic function and size:
  - Contractility is best determined using parasternal views.
  - 'Good' contractility: LV walls almost touch during systole and nearly obliterate ventricular cavity; anterior leaflet of mitral valve moves vigorously in parasternal long axis view.
  - 'Poor' contractility: minimal wall movement or change in ventricular cavity between systole and diastole.
  - Small ventricular cavity in hypovolemic conditions.
- Assess for right ventricular (RV) strain (Figure 4.3):
  - Classic sign of massive pulmonary embolus.
  - RV dilation: RV size exceeds LV size.
  - Paradoxical septal wall motion or 'D' sign: best seen in parasternal short view; normal LV is circular but increased RV pressure flattens or bows interventricular septum into LV during diastole.
  - *McConnell's sign*: RV dysfunction with characteristic sparing of apex; often described as 'invisible man jumping on trampoline at RV apex'.

BOTTOM LINE/CLINICAL PEARLS

- Ribs block US waves and obscure views of heart. Make fine adjustments by rotating and angling cardiac probe so the US beam is parallel to ribs.
- Epicardial fat pad may be mistaken for an effusion; it is most prominent anteriorly.
- Some views will be difficult to obtain in individual patients. Turning patient into left lateral decubitus position may improve views.

Inferior vena cava (ultrasonography)

Probe selection and orientation

- Use phased array 'cardiac' probe or curvilinear probe.
- Same screen/probe orientation as for subxiphoid view of heart.

Scanning technique

- Start with subxiphoid view of heart, then rotate probe 90° so probe indicator points cephalad.
- Slide probe slightly right of midline until IVC is visualized in longitudinal plane.
- Identify where IVC transitions into right atrium to confirm visualization of IVC versus abdominal aorta (Figure 4.4).
- Measure IVC diameter 2 cm caudal to junction of IVC and right atrium.
- Use M-mode on IVC to graphically visualize respiratory variation in IVC caliber.

Clinical application

- Estimate intravascular volume and monitor response to fluid challenges by evaluating IVC diameter and collapsibility (Table 4.3).
- Correlation between central venous pressure (CVP) and IVC diameter and percentage change with respiratory variation.
- If IVC diameter is <1 cm → higher probability of fluid responsiveness.
- If IVC diameter is >2.5 cm → lower probability of fluid responsiveness.
- IVC diameter between 1 and 2.5 cm → indeterminate probability.

Table 4.3 Intravascular volume estimation.

Intravascular volume status*	IVC caliber	IVC collapsibility	CVP
Volume depleted	Small (<1 cm)	>50%	<10 cmH_2O
Volume overloaded	Large (>2.5 cm)	<50%	>10 cmH_2O

* IVC distention with minimal respiratory variation may occur in clinical scenarios other than volume overload (e.g. cardiac tamponade).

BOTTOM LINE/CLINICAL PEARLS

- Do not mistake pulsatile abdominal aorta for IVC. If it is the IVC, the vessel can be seen entering the right atrium; also look for hepatic vein entering the IVC.
- 'Plump IVC' does not always indicate volume overload. Assess cardiac function prior to IVC to provide context for IVC findings.

Lung ultrasonography

Probe selection and orientation

- Use phased array 'cardiac' probe (adequate for majority of lung examinations).
- Use linear array 'vascular' probe for detailed exam of pleural surface.
- Point probe indicator toward patient's head (general radiology convention).

Scanning technique

- Position probe over rib interspace so rib shadows are on each side of US screen.
- Identify following normal lung findings (Figure 4.5 and Video 4.1):
  - Pleural line: shimmering echogenic line at top of screen.
  - Lung sliding: periodic movement of pleural line; represents movement of visceral and parietal pleura relative to chest wall.
  - A-lines: repetitive horizontal artifact resulting from reverberation of US waves between skin and pleural surface; space between A-lines equal to distance between probe head (on skin surface) and pleural line.
  - Seashore sign: graphical visualization of lung sliding in M-mode; often described as 'waves on a sandy beach' (waves represent motionless chest wall, sandy beach represents air-filled lung).
  - B-lines: vertical artifact arising from pleural surface; appears like laser beam that effaces A-lines and projects to bottom of screen. Usually do not see B-lines anteriorly; may see a few (1–3) posteriorly in dependent regions in normal scans.
- Slide probe vertically down chest wall to examine adjacent interspaces.
- Repeat this process in systematic fashion along anterior, lateral, and posterior chest wall.

Clinical application

- Assess for pneumothorax:
  - Absence of lung sliding plus absence of B-lines (Video 4.2).
  - Barcode or stratosphere sign: parallel horizontal lines indicating absence of lung sliding in M-mode (Figure 4.6).
  - Lung point sign: transition point – between border of pneumothorax and normal pleural interface – where intermittent lung sliding is visualized. It is pathognomonic and helpful in estimating size of pneumothorax.

Table 4.4 Features of cardiogenic pulmonary edema and non-cardiogenic lung injury.

Cardiogenic pulmonary edema	Non-cardiogenic lung injury
• Homogenous B-line distribution • Smooth pleural line • Absence of A-line pattern	• Non-homogenous B-line distribution • Irregular pleural surface

- Assess for pleural effusion:
  - Effusion appears as anechoic area usually in dependent areas; important to examine posterior chest wall in supine patient.
  - Lung flapping or jellyfish sign: collapsed lung floating in pleural effusion (Figure 4.7).
- Assess for pulmonary edema and consolidation (Table 4.4):
  - Diffuse B-lines (more than three in single field) is abnormal (Figure 4.8).
  - Consolidated lung appears isoechoic with liver, referred to as ‘hepatization’ (Figure 4.9).
  - Sonographic air bronchograms appear as punctuate hyperechoic foci.

BOTTOM LINE/CLINICAL PEARLS

- Do not mistake chest wall for pleural line.
- While absence of lung sliding suggests pneumothorax, it can occur in a variety of other situations such as pulmonary fibrosis and contusions, bullous emphysema, mainstem intubation, and pleurodesis.
- Routinely check for lung sliding before and after any transthoracic procedure to evaluate for iatrogenic pneumothorax, e.g. central venous access.
- Examining for pleural effusion with head of bed elevated may improve sensitivity as fluid will accumulate above diaphragms.

Abdomen

Probe selection and orientation

- Use phased array ‘cardiac’ probe or curvilinear probe.
- Point probe indicator toward patient’s right side or head (general radiology convention).

Scanning technique

- *Morison’s pouch with hemothorax view*. Position probe with indicator pointing toward patient’s head at the right mid-axillary line near the lower intercostal spaces. Identify the liver and kidney. Slide probe cephalad to look for pleural fluid and caudal to look for intraperitoneal free fluid (Figure 4.10).
- *Splenorenal recess with hemothorax view*. Position probe with indicator pointing toward patient’s head at the left posterior–axillary line near the lower intercostal spaces. Identify the spleen and kidney. Slide probe cephalad and caudal similar to Morison’s pouch view.
- *Bladder view*. Position probe just above pubic bone and angle caudally. Point indicator toward patient’s right side to obtain transverse view and toward head to obtain sagittal view. Rock the probe to scan entire bladder and look for free fluid (Figure 4.11).
- *Renal view*. Locate right and left kidneys using same landmarks as Morison’s pouch and splenorenal recess views, respectively. Rock the probe to scan entire kidney.
- *Abdominal aorta view*. Position probe high in the epigastrium with indicator pointing toward patient’s right to obtain transverse view. Identify the aorta on patient’s left and IVC on patient’s right side. Scan aorta starting in the epigastrium and towards the umbilicus until the iliacs come into view. Obtain at least three transverse views and measure aortic diameter using calipers. Point probe toward patient’s head to obtain sagittal view from celiac to illiacs.

Clinical application

- Assess for intraperitoneal free fluid:
  - Morison's pouch is the most dependent area in the upper peritoneum when a patient is supine.
  - The pelvis is the most dependent area of the peritoneum and the most likely place to see free fluid.
- Assess the urinary tract:
  - To evaluate anuria/oliguria, perform a renal and bladder scan to look for urinary tract obstruction.
  - Hydronephrosis appears as an anechoic area or 'bear paws' at center of kidney.
  - Degree of hydronephrosis is related to degree of urinary tract obstruction.
  - Distended, fluid-filled (anechoic) bladder indicates bladder outlet obstruction.
  - Bilateral hydronephrosis with normal/empty bladder indicates compression of both ureters.
- Assess for aortic aneurysm:
  - Abdominal aortic aneurysm is defined as aortic diameter >3.0 cm.

BOTTOM LINE/CLINICAL PEARLS

- Scan thoroughly in multiple windows to evaluate for intraperitoneal free fluid.
- Do not mistake renal cysts for hydronephrosis. Cysts are generally located at the periphery of the kidney.
- Aneurysms often contain thrombi. Measure aorta from outer wall to outer wall to avoid mistaking thrombus for aortic wall and obtaining a falsely decreased aortic diameter measurement.

Leg vein ultrasonography

Probe selection and orientation

- Use linear array 'vascular' probe.
- Point probe indicator toward patient's right side (general radiology convention).

Scanning technique

- To optimize patient positioning, slightly abduct and externally rotate hip.
- Start by placing probe in transverse position along inguinal crease and locating common femoral vein (CFV).
- Compress vein firmly with transducer. If vein does not completely collapse despite applying enough pressure to deform the artery, a clot is likely present.
- Scan down medial thigh toward bifurcation of the CFV into the superficial and deep femoral veins. Compress every centimeter to systematically evaluate for clot.
- Lastly, place probe behind knee in popliteal fossa and locate popliteal vein which lies superficial to the artery. Compress vein firmly to assess for clot.

Clinical application

- Assess for leg vein thrombosis (Figure 4.12).

BOTTOM LINE/CLINICAL PEARLS

- Elevate head of bed or place patient in reverse Trendelenburg to maximize venous distension of lower extremities.
- Do not assume an anechoic lumen is a patent lumen. An acute clot may be anechoic.
- Baker's cyst or lymph nodes may be mistaken for clot.

Table 4.5 RUSH exam protocol.

RUSH exam	Hypovolemic shock	Cardiogenic shock	Obstructive shock	Distributive shock
Pump	Hyperconstractile heart Small heart size	Hypoconstractile heart Dilated heart size	Pericardial effusion RV strain Hyperconstractile heart	Hyperconstractile heart (early sepsis) Hypoconstractile heart (late sepsis)
Tank	Flat IVC Flat IJV Peritoneal fluid Pleural fluid	Distended IVC Distended IJV Lung rockets Pleural effusions, ascites	Distended IVC Distended IJV Absent lung sliding (PTX)	Normal/small IVC Normal/small IJV Pleural fluid (empyema) Peritoneal fluid (peritonitis)
Pipes	AAA Aortic dissection	Normal	DVT	Normal

Management/treatment algorithm

- Multiple point-of-care US protocols have been proposed for the rapid diagnosis of undifferentiated shock.
- The Rapid Ultrasound in SHock (RUSH) exam is a stepwise resuscitative US protocol developed in 2010 that incorporates many of the core US principles proposed and validated in prior studies (Table 4.5).
- The RUSH exam simplifies bedside physiologic assessment into three steps: evaluation of 'the pump,' 'the tank,' and 'the pipes.'

Reading list

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Seif D, et al. Bedside ultrasound in resuscitation and the rapid ultrasound in shock protocol. Crit Care Res Pract 2012;2012:1–14.

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Suggested websites

www.emcrit.org/rush-exam/original-rush-article/
www.sonoguide.com

Images

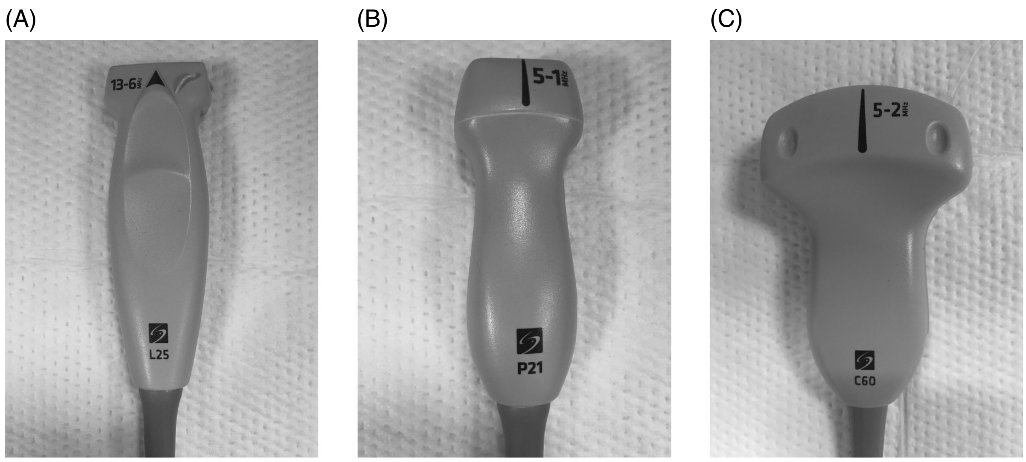

Figure 4.1 Probe types. (A) Linear. (B) Phased array. (C) Large curvilinear.

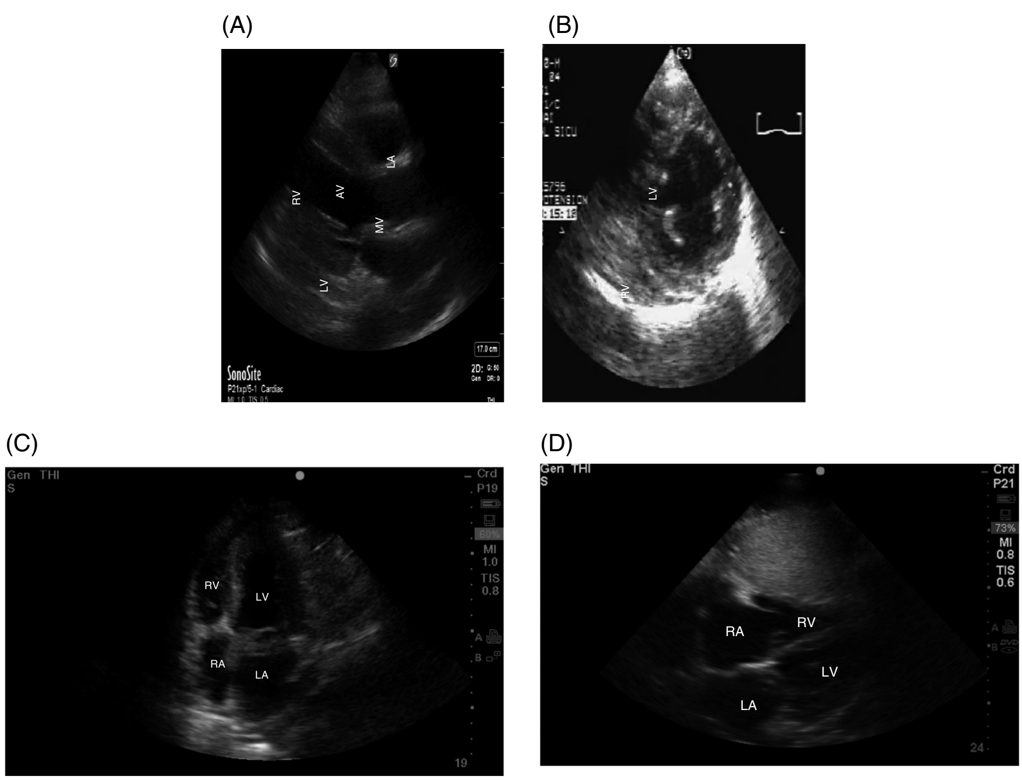

Figure 4.2 Standard bedside ECHO views. (A) Parasternal long axis, systole; aortic valve open, MV closed. (B) Parasternal short axis, mid-papillary muscle level. (C) Apical four chamber view. (D) Subxiphoid view.

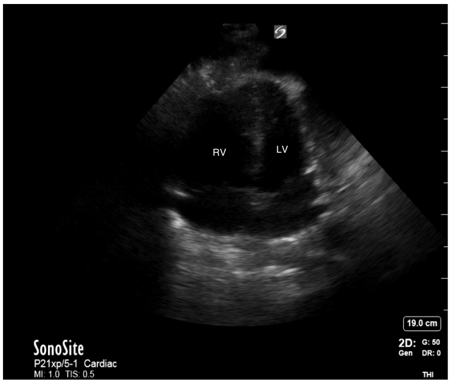

Figure 4.3 Right ventricular strain. RV size exceeds LV size; RV pressure flattens or bows interventricular septum into LV during diastole (apical four chamber window).

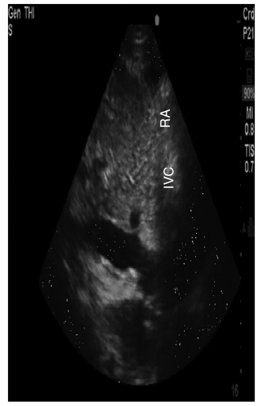

Figure 4.4 IVC transitions into RA to confirm visualization of IVC versus abdominal aorta.

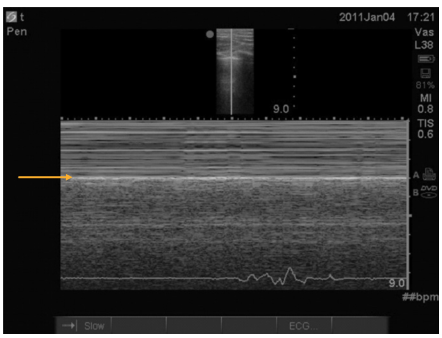

Figure 4.5 M-mode chest with 'seashore' signal. The thicker first horizontal line (arrow) is the pleural line. Above the pleural line are (normal) horizontal lines due to the chest wall. Below the pleural line, where the lung is present, note the 'sandy' appearance diagnostic of lung sliding. Lung sliding rules out a complete pneumothorax.

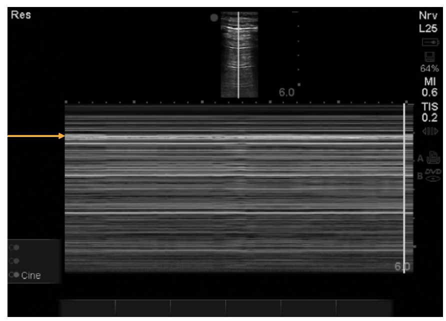

Figure 4.6 M-mode chest with the 'barcode' or 'stratosphere' sign. The thicker first horizontal line is the pleural line. Above the pleural line are (normal) horizontal lines due to the chest wall. Below the pleural line, where the lung should be present, note the (abnormal) presence of straight horizontal lines indicating an absence of lung sliding. Absent lung sliding may indicate a pneumothorax or intact lung with pleurodesis.

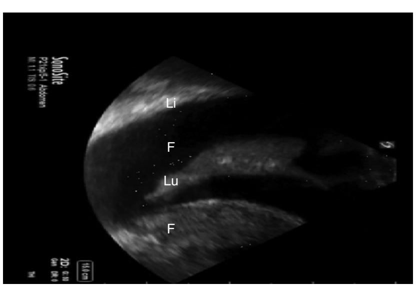

Figure 4.7 Pleural effusion. Anechoic fluid (F) surrounding lung (Lu). Note the diaphragm and liver (Li) below. In a real time video, the lung will move dynamically within the anechoic fluid. This is called 'lung flapping.'

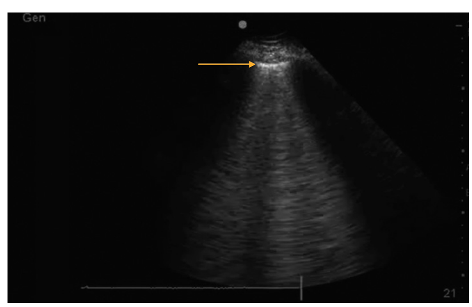

Figure 4.8 Pulmonary edema. Note the vertical lines (B-lines) descending from the pleural line (arrow) and continuing to the end of the screen.

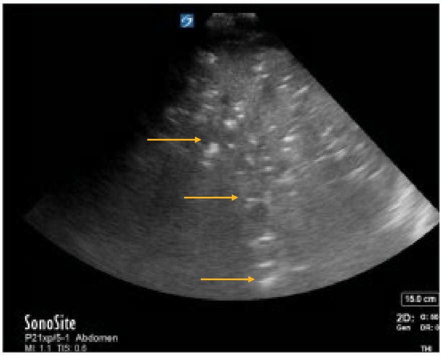

Figure 4.9 Consolidation. Ultrasound of the right lung demonstrating numerous air bronchograms (arrows) that appear as echogenic areas – circular (transverse) or longitudinal.

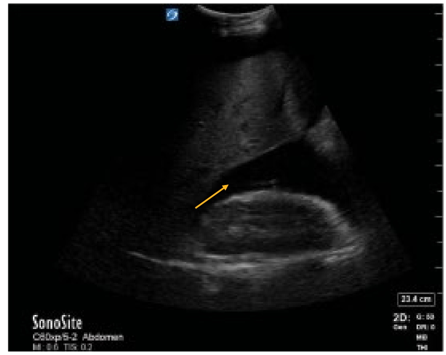

Figure 4.10 The potential space between the liver and right kidney is called Morison's pouch. In this image, the anechoic space between the liver and kidney (arrow) indicates the presence of free intra-abdominal fluid.

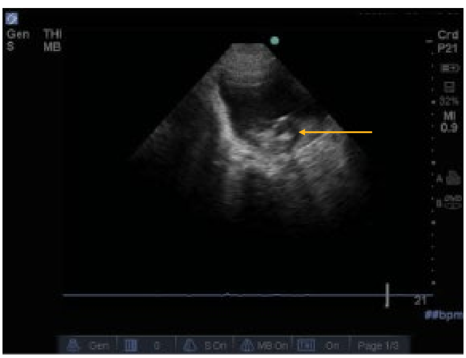

Figure 4.11 Bladder view (transverse orientation) with a Foley (balloon filled with water (anechoic), arrow). In the presence of a Foley, the bladder should be empty. If the bladder is not empty, look for an obstruction in the Foley catheter which may need to be flushed or replaced.

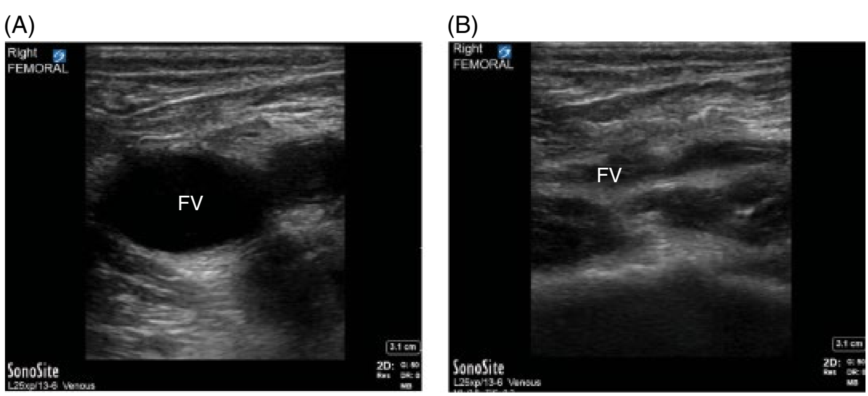

Figure 4.12 Assess for leg vein thrombosis. See text for scanning sequence. (A) Without compression. The vein appears anechoic without echogenic material within. (B) With compression via the US probe the femoral vein (FV) collapses. This indicates the absence of a thrombus in the FV at this level.

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This includes multiple choice questions and Videos 4.1 and 4 2.

with website

CHAPTER 5

Bronchoscopy

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OVERALL BOTTOM LINE

- In patients with respiratory insufficiency/emergent evaluation with bronchoscopy can prevent morbidity and mortality.
- Bronchoscopy provides a means to evaluate the airways; it can be both diagnostic and therapeutic.
- It is essential that all intensivists have an understanding of bronchoscopy and be able to perform this life-saving procedure in critical situations.
- Some life-threating situations where bronchoscopy can be used are:
  - Difficult intubations.
  - Complete lung atelectasis secondary to mucus impaction.
  - Lavage for aspiration of blood and stomach contents.
  - Removal of foreign objects.
  - Hemoptysis.

Introduction

Bronchoscopy is a procedure utilized to visualize the airways. There are three types:

- Flexible bronchoscopy (or white light bronchoscopy) uses a small (5–6 mm diameter) flexible instrument that can access the distal airways. This requires conscious sedation.
- Rigid bronchoscopy is usually done in the OR, using a rigid instrument larger than the flexible scope. It requires general anesthesia and can only access the proximal airways.
- Virtual bronchoscopy uses images to reconstruct a 3D picture of the airways. This is a non-invasive procedure.

In this chapter we will be discussing flexible bronchoscopy which is used by the intensivist in the ICU on critically ill patients.

The bronchoscope

- The handle on the top of the bronchoscope is for up and down movement of the bronchoscope tip; the tip moves up and down in one plane. The right thumb is used to flex and re-flex the handle. The upward movement of the handle moves the tip down and vice versa.
- The protruding gray color knob on top is for suctioning of fluid. The right index finger is used on the suction port. Other movement is achieved by movements at the wrist.
- The protruding gray color knob second from the top is for instillation of fluid and accessories (working channel).

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Indications

- Atelectasis.
- Large volume aspirate for lavage.
- Non-resolving pneumonia, to collect samples.
- Percutaneous tracheostomy placement.
- Endotracheal tube (ETT) placement with difficult intubations.
- Evaluation of tracheostomy tube or ETT.
- Aid to relieve thick secretions/mucus impaction, mostly in spinal cord injury patients (this is done frequently prior to extubation of a ventilated patient).
- Hemoptysis.
- Small foreign body removal.
- Suspected airway obstruction, e.g. tracheal stenosis, endobronchial lesions.

Pre-procedure

- Obtain informed consent (in ICU this is usually from the health care proxy).
- NPO for at least 4–6 hours prior to the procedure if possible in non-emergent or non-intubated patients; tube feeds should be held before the procedure.
- Perform time out.
- Set up: done in a monitored setting with ECG recording, BP monitoring, O_2 saturation monitoring, bronchoscope, accessories for the bronchoscope (e.g. brush, forceps, balloon), bronchoscopic adaptor (ventilator and bronchoscope can both be use at the same time), specimen collecting system, saline (some should be ice cold), alcohol, slides, epinephrine, lidocaine (solution and gel), oxygen, ETT, oral piece, gauzes, port syringes, suctioning system, IV fluid, sedative, analgesics, lubrication, vasopressor agents, and resuscitation medications (e.g. naloxone) available if needed.
- Protective wear available.
- Personnel: bronchoscopist, bronchoscopist assistant (to help with use of forceps, brush, ETT stabilization, etc.), critical care nurse, and respiratory therapist.
- Lab work: generally not needed but PTT and INR in cases of hemoptysis.
- In non-intubated patients, the nares/airways should be anesthetized with aerosolized lidocaine and lidocaine gel.
- In intubated patients, the ETT should be at least 7.5–8 mm in diameter for the typical bronchoscope to pass. ETT change may be necessary.
- In intubated patients, the airway can be sprayed with lidocaine or the lidocaine can be nebulized before the start of the procedure. About 400–600 mg can be safely used for the entire procedure.
- Sedatives should be given for moderate sedation in non-intubated patients. Typical medications are midazolam (noted to decrease salivation during bronchoscopy) or propofol used with fentanyl (to decrease coughing). For intubated and sedated patients, an increase in the baseline sedative(s) is required.
- Generally patients should be placed on 100% oxygen. In the ICU, most patients requiring bronchoscopic procedures are intubated.

Bronchoscopy procedure

- Adjust the height of the bed where your non-dominant hand can reach the point of entry of the bronchoscope (mouth, nose, ETT, or tracheostomy device) and the other arm can be fairly well extended upright to control the bronchoscope.
- Keep the bronchoscope in the center of the airways. If suction is applied while the tip of the bronchoscope is on the airway wall, ecchymosis or erythema will occur.

- Examine the lungs by advancing the lubricated bronchoscope through the nares towards the vocal cords, or threading it through an ETT (Video 5.1). It should be advanced slowly, ensuring that there is no resistance. See Figure 5.1 for the segmental and lobar divisions of the lungs.
- The anterior larynx should be seen with the cartilaginous rings and the posterior should be seen flat.
- The vocal cords should not be seen in an intubated patient since the ETT should be through the vocal cords and the ETT tip sits about 3–4 cm above the main carina. (If the vocal cords are seen, the ETT is above the cords and would need to be advanced.)
- The bronchoscope is advanced to the main carina (Video 5.2). The tracheal rings are on the anterior aspect. If the bronchoscopist is doing the procedure from behind the patient, the right main bronchus will be on the right and the left main bronchus will be on the left, as in Figure 5.1.
- The bronchoscope can then be advanced to the right mainstem bronchus. At this point the bronchus intermedius will be seen at 3 o'clock and the right upper lobe (RUL) bronchus will also be seen (Figure 5.2). In most patients the RUL will have three orifices: the apical, anterior, and posterior segments (called the Mercedes Benz sign). However, in <3% of patients four orifices will be seen.
- Now withdraw the scope from the RUL bronchus and return to the bronchus intermedius. Straight ahead the right lower lobe (RLL) will be seen. The superior segment of the RLL is opposite to the right middle lobe (RML). The RML has the shape of a letter 'D' (called the fish mouth sign).
- Withdraw the bronchoscope to the main carina before advancing it towards the left bronchus, which is longer than the right main bronchus. Once in the left mainstem bronchus a 'secondary carina' can be seen. This can be distinguished from the main carina by the smaller diameter of the lumens and the absence of tracheal rings.
- The secondary carina divides the left upper lobe and left lower lobe.
- Samples can be collected in the infected lobe/s after visualization of the presumed uninfected lung/lobes/segments. The bronchoscope should be directed to the lobe/segments in question and wedged, then saline squirted in aliquots of 10–15 mL. The saline is then suctioned into the sample containers.
- If a lesion is seen, samples can be obtained by using a brush/forceps. Slides can be made from the samples or the brush can be washed and the sample sent for cultures/cytology. Biopsies of lesions are usually deferred to a pulmonologist.
- If active intrabronchial hemorrhage (Video 5.3) is noted then the source of bleeding can be controlled by squirting epinephrine or ice-cold saline at the site and holding the bronchoscope to tamponade the bleeding. A catheter with a small balloon can be inserted and inflated at the end of the bronchoscope that may temporize the bleeding. In cases of massive hemoptysis, the non-bleeding lung can be intubated allowing the bleeding lung to collapse. Rigid bronchoscopy may be required. Options for the control of bleeding include interventional radiologic procedures, bronchial artery embolization, and surgery.
- The flexible bronchoscope fits well in a 7.5 mm ETT and can be used to visualize and be inserted into the trachea for difficult intubation.
- Forceps and basket can be inserted through the flexible bronchoscope working port and this can assist with the removal of small foreign objects in the airway.
- Bedside tracheostomy can be done in the ICU with the aid of bronchoscopic visualization.

Common complications

Pre-procedure

- From anesthetic: laryngospasm, bronchospasm.
- From sedative: hypotension, bradycardia (propofol).

Procedure

- Laryngospasm or bronchospasm.
- Hypoxemia.
- Fever.
- Hemoptysis.

Management of complications

Complication	Treatment
Hypotension	Fluids, vasopressors
Laryngospasm	Lidocaine (topical)
Bronchospasm	Bronchodilators
Hypoxemia	If patient is not on 100% O_2 increase O_2 If on 100% O_2, remove bronchoscope until saturation increases
Hemoptysis	Usually minimal but for moderate hemoptysis use local epinephrine, tamponade, intubation of the non-bleeding lung
Fever	May occur for 24 hours post-procedure; treatment is rarely needed but antipyretics can be given

Follow-up

A CXR is generally not required after airway clearance, visualization, and lavage, but is often done to assess the efficacy of treatment for atelectasis.

Reading list

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Images

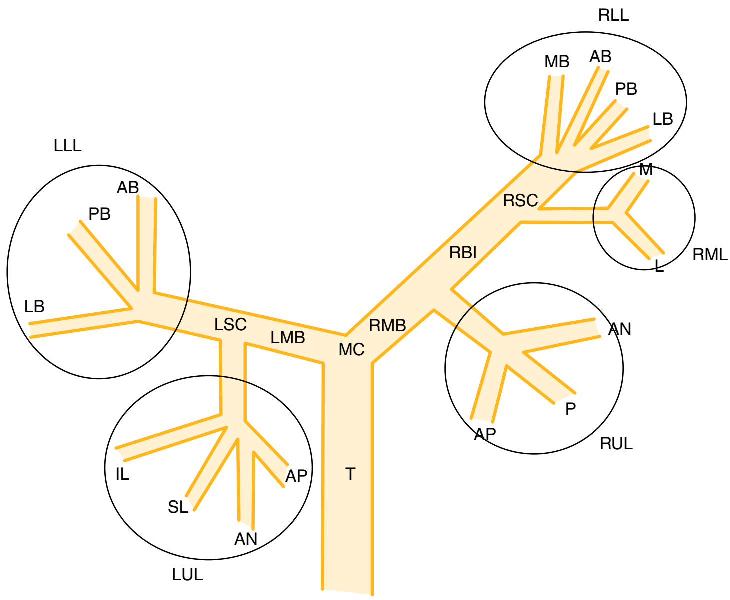

Figure 5.1 Simplified diagram of the bronchial tree (not drawn to scale), which is easily visualized by the bronchoscopist standing at the head of the bed, behind the patient. T, trachea; MC, main carina. *Right bronchus*: RMB, right mainstem bronchus; RBI, right bronchus intermedius; RSC, right secondary carina; RUL, right upper lobe: AN, anterior; AP, apical; P, posterior; RML, right middle lobe: L, lateral; M, medial; RLL, right lower lobe: AB, anterior basal; LB, lateral basal; MB, medial basal; PB, posterior basal. *Left bronchus*: LMB, left mainstem bronchus; LSC, left secondary carina; LUL, left upper lobe: AN, anterior; AP, apico-posterior; IL, inferior lingula; SL, superior lingual; LLL, left lower lobe: AB, anterior basal; LB, lateral basal; MB, medial basal.

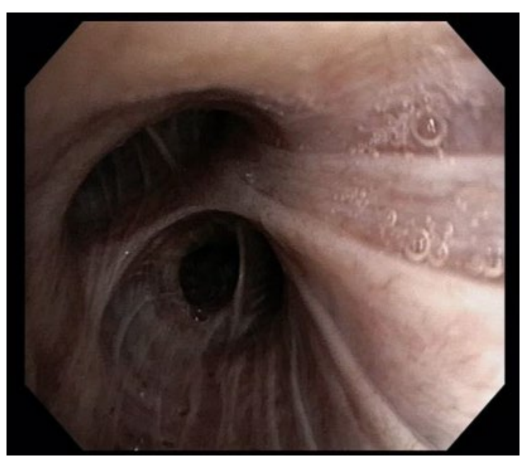

Figure 5.2 Right upper lobe. (See website for color version.)

Additional material for this chapter can be found online at: www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions and Videos 5.1, 5.2 and 5.3. The following image is available in color: Figure 5.2.

with website

CHAPTER 6

Bedside Percutaneous Dilational Tracheostomy

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OVERALL BOTTOM LINE

- The bedside percutaneous dilational tracheostomy (PDT) with a minimal tracheostomy incision utilizes the Seldinger technique and gradual dilation to insert the tracheostomy.
- PDT is a safe procedure in the critical care setting and should be first choice when available. Its use is more cost-effective and trends towards fewer complications compared with open surgical tracheostomy.
- Proper selection of the bedside candidate requires a hemodynamically stable patient with no bleeding diatheses and normal neck anatomy.
- PDT is associated with less bleeding than open tracheostomy. Patients on anticoagulation or with severe derangements of INR or platelet count may either be supplemented with the appropriate blood products or deferred until stable for the procedure.
- Bronchoscopic guidance is often used during bedside tracheostomy procedures, but is not routinely required since it has not demonstrated better outcomes. Those not routinely using a bronchoscope may reserve its use for difficult cases.

Background

- Surgical tracheostomy has been performed since 1909.
- Percutaneous tracheostomy using the Seldinger technique allows tracheostomy placement at the bedside in the ICU.

Tracheostomy benefits (Table 6.1)

- Tracheostomy is considered for the patient who is expected to require a prolonged course of mechanical ventilation or requires an artificial airway for obstruction or secretion clearance.
- For patients requiring mechanical ventilation for more than 2 weeks, it is believed that tracheostomy may be beneficial in avoiding continued injury to the vocal cords.
- Tracheostomy may be better tolerated and allow a reduction of sedation. As a consequence it facilitates physical therapy, nursing care, and transfer of the ventilated patient out from the ICU setting.
- Weaning from mechanical ventilation is also expedited due to the decreased work of breathing from a reduction of airway resistance and dead space.
- Other benefits include patient comfort such as the initiation of oral intake, communication, and mobility, and possibly fewer respiratory infections.

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Table 6.1 Risks and benefits of tracheostomy.

Benefits	Risks
Secure airway Expedite weaning or transfer from ICU Facilitate nursing care Communication Patient comfort and eating Mobility/physical therapy	Pneumothorax Tracheo-innominate artery fistula

Early versus late tracheostomy

- Early tracheostomy is variably defined, and generally performed within 4 days of intubation.
- Earlier tracheostomy is considered if the likelihood of intubation is recognized to be prolonged beyond 2 weeks.
- Patient discomfort secondary to translaryngeal intubation and multiple failed extubation attempts may also support earlier tracheostomy.
- The benefits for earlier intervention are not clear. In some studies, such as in patients with traumatic brain injury or subarachnoid hemorrhage, reductions in length of stay (LOS) and pulmonary infections have been seen. However, in these neurosurgical populations, patients are often considered for earlier tracheostomy due to mental status issues and fear of weaning. A review and meta-analysis also indicated early tracheostomy placement reduced the duration of mechanical ventilation and hospital stay.
- There is no definitive mortality benefit for early tracheostomy.
- In general, the decision for tracheostomy should begin with an evaluation of the patient within a week of intubation as to the likelihood of extubation in the upcoming week. The first week's course is often predictive of ventilator dependency.

Open surgical tracheostomy versus bedside PDT

- Bedside approaches are performed either as open, cut-down procedures or via PDT using the Seldinger method. The Seldinger method is essentially a blind procedure done at the bedside.
- The primary advantages to the bedside approach are the more efficient use of OR time and the consequent cost savings, which include those of patient transportation and general anesthesia.
- Further advantages of PDT include smaller incisions, decreasing the likelihood for poor wound healing, scarring, and peristomal bleeding, and reduced local site infections. The procedure can also be more timely.
- LOS in the ICU as well as time to placement of the tracheostomy is significantly shortened with PDT, suggesting further cost savings when using bedside procedures.
- Most importantly, major complications and mortality are similar between PDT and open surgical tracheostomy. This is regardless of whether the bedside procedure is PDT or open.

Risk factors

- Consent for procedure includes the risks of: pneumothorax (PTX), tracheo-innominate artery fistula, airway damage and stenosis, bleeding, infection, and death.
- Mortality of this procedure is less than 1%, while major morbidity is 5–10%.
- Bleeding with PDT is minimal. Prior ultrasonography of the trachea assesses for any smaller crossover veins, which are uncommon but may cause bleeding.
- PTX is a serious complication that can be fatal if not immediately recognized and treated. It presents with difficulty in ventilation, hypotension, and/or oxygen desaturation due to tension PTX, and often within minutes of the tracheotomy. Chest tube kits should be readily available during these procedures.

- Innominate artery fistula can either be a relatively early or late event, and is a surgical emergency. A surgeon should immediately assess any bleeding from the tracheostomy site since any manipulation of the tube may undo the (possibly life-saving) tamponade effect on the fistula.
- Tracheal stenosis and tracheomalacia can be late complications at the tracheostomy site.

Selection of candidates for bedside PDT

Patient's history and clinical status

- Indication for tracheostomy: failed weaning/extubation, relief of airway obstruction or secretions.
- Review surgical history for prior neck surgery, tracheostomy, or radiotherapy to the anterior trachea/neck.
- Hemodynamic stability, stable cardiac condition.
- Lack of bleeding, intact coagulation profile (preferably INR <1.5 and platelet count >50 000).
- Absent severe sepsis.
- In making the decision for PDT, it is important to keep in mind that this is an otherwise elective procedure so care must be taken to avoid potential complications.

Examination of candidates

- The ideal patient for PDT has a well-defined anatomy – a long thin neck, with palpable tracheal spaces that can be hyperextended safely. The first criterion safeguards the anatomy for this essentially blind procedure: namely that the tracheotomy is done between the third and fourth tracheal cartilage. The splaying of the cartilage rings is key in the proper positioning of the patient for PDT. In general, patients with recent neck injuries, morbidly obese necks, and previous tracheostomy or neck irradiation are contraindicated for bedside PDT. Anterior infection or burns of the neck, as well as goiter or masses, are also contraindications. Such patients are better relegated to an open surgical procedure.
- If cervical spinal injury is present, PDT is contraindicated, and if in question, neurosurgical or neurological clearance for hyperextension would be necessary. Patients whose neck cannot be hyperextended such as patients with cervical osteoarthritis are also better treated in the OR. Note: PDT is not meant for acute emergency tracheotomies where the more cephalad cricothyroid membrane is the anatomy of choice for the tracheotomy.
- The physical exam concentrates on identifying adenopathy, burns, infection, masses, scars (previous surgery or old tracheostomy scar), trauma, and thyromegaly (goiter). Review the skin surface for small veins to avoid lacerating during the procedure. If available, US examination can assist in identifying any aberrant vasculature or other anomalies that may defer PDT to an operative procedure.
- Assess the extent of neck hyperextension. Is the neck short and thick? Is extension not possible due to cervical arthritic changes? Inability to palpate the tracheal anatomy due to obesity or short neck length, and/or inability to hyperextend allowing at least two finger breaths above the sternal notch would contraindicate the procedure.
- Patients with obese necks may have successful PDT although they may require bronchoscopic assistance, cut down, and longer tracheostomy tubes**.** The patient must be hemodynamically stable as significant sedation and/or paralysis may be needed for the procedure. The most common reason to prolong the PDT procedure is sedation-related hypotension necessitating intravenous fluids or vasopressors. Assessing the degree of hyperextension earlier will require full sedation, indicating the need for fluid resuscitation prior to the procedure. Also be aware that bradycardia due to vagal effects may worse.
- The patient should have satisfactory gas exchange, not requiring high PEEP.

Relative contraindications

- Anatomic:
  - Previous tracheostomy, surgery.
  - Skin infection or burns.

  - Short obese neck, goiter, adenopathy, mass.
  - Spinal injury, lack of hyperextension.
- Physiology:
  - Bleeding diathesis.
  - High O_2 requirements (high PEEP).
  - Hemodynamically unstable.
  - Poor nutrition status.

PDT procedure

- The procedure (Video 6.1) can be performed in a critical care unit with continuous monitoring.
- Patient must be NPO for at least 6 hours and subcutaneous heparin is withheld prior to the procedure.
- All appropriate sterile precautions must be employed, using sterile gowns, masks, gloves, and drapes along with the PDT kits.

Procedure without bronchoscopic guidance

- Start by providing appropriate sedation. Fentanyl and propofol are given to the patient, ideally as an infusion, and titrated so the patient is motionless, without cough or gag, when palpating the trachea. If hypotension develops, the decision to provide fluids, vasopressors, and to continue the procedure are made jointly between the surgeon and anesthesiologist. Paralysis is not a requirement for this procedure and is reserved for those patients with movement despite adequate sedation.
- After sedation is achieved, a roll is placed midline under the scapula to facilitate hyperextension of the neck (Figure 6.1). The head is ideally hanging in air unless you place a pillow underneath. This positioning may arouse the patient if they are not adequately sedated.
- Prepare the PDT kit (Figure 6.2): test the tracheostomy tube (TT) cuff for patency, and remove all air after testing; adequately lubricate the TT and trochanter; prepare the guidewire; fill the subcutaneous and catheter syringes with 1% lidocaine/epinephrine; and hydrate the dilator with saline flush.
- Increase the oxygen to 100% FiO_2; suction the endotrachea (ET) and mouth for secretions; clean the anterior neck and inject lidocaine/epinephrine subcutaneously two fingers above the sternal notch and midline. The respiratory therapist then deflates the ETT cuff while increasing the tidal volume to compensate for creating a leak (add 100 mL to the tidal volume).
- Palpate your needle puncture point at two fingers above the sternal notch and two cartilage rings below the cricoid cartilage. The needle is advanced in a *perpendicular position midline* on the trachea.
  - At the midline position of the trachea there is no muscle or vasculature. The sternocleidomastoid, sternohyoid, and sternothyroid are lateral. A puncture too high will result in difficulties with the cartilage; too low may result in erosion of the tracheostomy tube into the innominate artery creating a fistula.
- Advance the needle while pulling on the syringe filled with 1% lidocaine and epinephrine. When air is drawn into the syringe you have entered the trachea.
  - Aspiration of air confirms intraluminal tracheal placement. Entering the ET is a possibility; however it would require an extraordinary effort in piercing during the needle insertion. More likely you are in the trachea where the needle tip may be scratching the ET surface. The cuff may be ruptured at this point, but you should simply proceed. Adding to the tidal volume earlier should maintain ventilation.
  - Immediately 'anchor' the needle by placing your fingers at the junction of the needle and the skin of the neck to avoid dislodgment. Inject 5 mL of the 1% lidocaine/epinephrine solution.
  - Repeatedly reaffirm placement by demonstrating air bubbles during the procedure, especially if there is dislodgment from movement or otherwise. At any time if the location of needle is of concern start the procedure again, including palpating the trachea as above.

- Once the needle is touching the ET, the respiratory therapist pulls the ET back and forth which leads to tugging the needle in your fingers and affirming your position on the ET (Figure 6.3A).
  - The ET is then gradually pulled to the 20 cm mark or when you no longer feel the ET any more (Figure 6.3B), usually between 18 and 19 cm.
- Angle the needle caudally and pass the catheter. It should pass easily into the trachea.
  - If there is immediate resistance to advancing the catheter, you may not be in front of the ET, or possibly in a blind pouch. Return the needle to the perpendicular position; reaffirm position with air bubbles and have the respiratory therapist pull the ET slightly further cephalad. Retry passing the catheter as above.
  - The guidewire is now advanced into the trachea and should pass freely, inducing a cough when at the bifurcation. At this point, bronchoscopic or US confirmation can be performed (Figure 6.4).
- Using the scalpel, make a perpendicular cut longitudinally, next to the guidewire, above and below it. The single straight dilator follows, opening the tracheotomy, after which blood-tinged secretions may be seen bubbling through the incision. The plastic guidewire is placed over the metallic guidewire followed by the tapered dilator. The tapered dilators are marked to identify the level of dilation fitting the sized tracheostomy tube to be placed; proceed slowly with continued effort as you are dilating.
  - Ultrasonography prior to the procedure reviews the anatomy and assesses for anomalous vasculature that risks bleeding. It may also be of benefit in confirming the guidewire presence in the tracheal lumen. This is especially helpful if any questions arise during the procedure, so ultrasound should be available at the time of the procedure. This can also be done by bronchoscopy.
- Once fully dilated, the TT is inserted over the guidewire left in place once the dilator was removed. Again, maintaining the patient in the fully extended position is key to performing this step smoothly.
- Remove the trochanter from the TT, replace it with the inner cannula and connect to the ventilator. Do not extubate unless the patient is receiving full tidal volumes on the ventilator (remember air escaping from the ET may falsely diminish tidal volumes); listening to breath sounds and assessing O_2 saturation and end-tidal CO_2 will help verify TT placement.
- Remove the ETT, suture the TT in place and order a CXR to rule out PTX.

Bronchoscopic assistance

- The use of bronchoscopic guidance during tracheostomy is not routinely required and in at least one study did not result in better outcomes**.**
- It allows for positioning of the ETT and the placement of the needle under direct visualization.
- Bronchoscopy may be of more use in complicated cervical collar patients or the obese; or acutely if uncertainties arise during the procedure.
- The advantages of bronchoscopy include: real-time needle-tip localization during the procedure with less needle punctures; confirmation of endoluminal placement and supracarinal measurement; and if there is dislodgment of the ETT or TT during the procedure it can guide replacement.
- The disadvantages include: additional equipment and personnel (bronchoscopist) and greater cost. Bronchoscopy can obstruct the airway with possible impaired ventilation.

Management of complications

- Pneumothorax: in the event of deterioration from a diagnosed or suspected PTX, immediately place a needle anteriorly between the first and second ribs, and bilaterally unless unilateral PTX is obvious.
- PTX can also present later, which is why a CXR always follows the procedure. If pneumothorax is present, a chest tube is required to prevent the development of tension pneumothorax.

Follow-up

- Standard tracheostomy care and gradual weaning from the ventilator is followed.
- De-cannulation is considered when the patient is breathing spontaneously without mechanical ventilation for a specified period of days, demonstrates reduced secretions, is able to cough secretions through the mouth, and has a patent airway.

Reading list

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Images

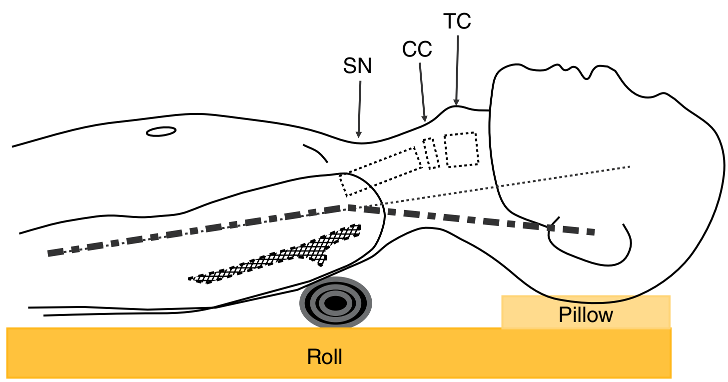

Figure 6.1 Patient positioning for tracheostomy. Place 'roll' under shoulder blades to maximize neck extension. Place a pillow under the head until you are ready to start. TC, thyroid cartilege; CC, cricoid cartilage; SN, suprasternal notch.

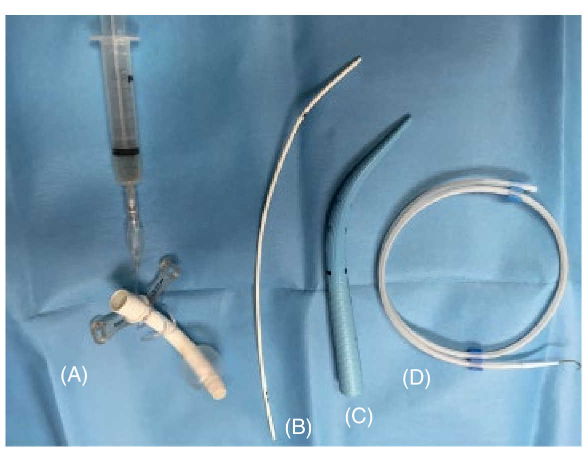

Figure 6.2 The essentials found in most percutaneous tracheostomy kits. (A) Tracheostomy tube with cuff inflated. (B) Plastic guidewire sheath with bulge at the top end to avoid posterior trachea injury from the dilator. (C) Tracheotomy tapered dilator. (D) Guidewire.

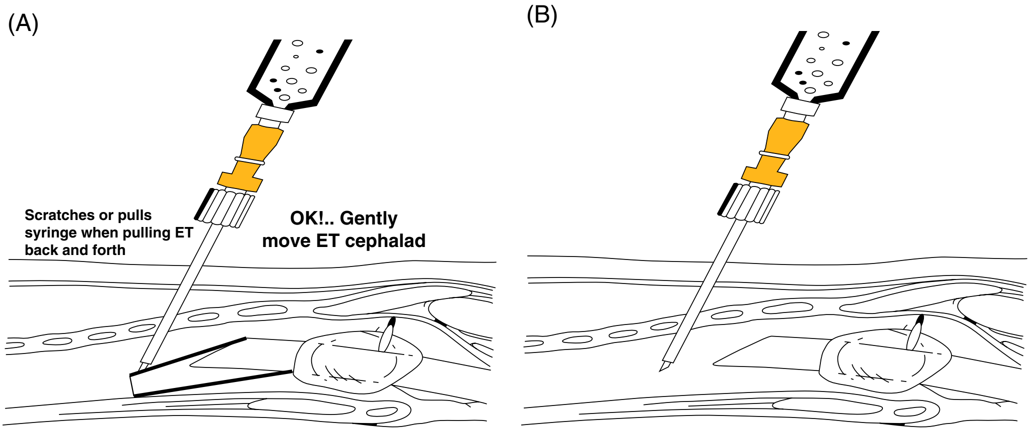

Figure 6.3 How to avoid scraping the ET. (A) Needle scraping the ET. (B) Gently move ET cephalad.

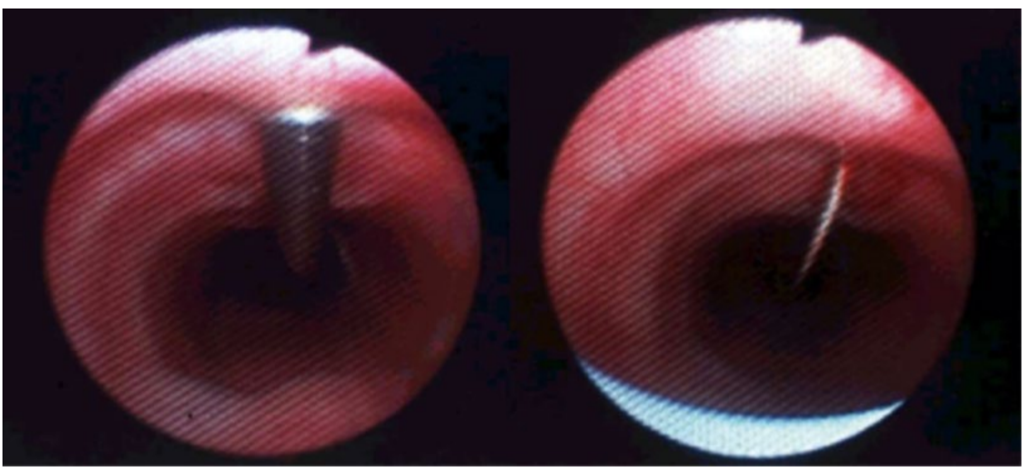

Figure 6.4 Needle and guidewire. (See website for color version.)

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions and Video 6.1. The following image is available in color: Figure 6.4.

with website

CHAPTER 7

Nutritional Support and Total Parenteral Nutrition

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OVERALL BOTTOM LINE

- Critically ill patients have increased metabolic demands and are vulnerable to developing malnutrition.
- Nutritional support should be started early to minimize morbidity and mortality.
- Both under- and overfeeding have deleterious effects on the patient's health.
- Enteral nutrition is preferred over parenteral nutrition where possible.
- Nutritional support requires a dedicated team and close monitoring to avoid infectious and metabolic complications.

Background

- Patients in the ICU are faced with unique challenges predisposing them to a malnourished state. This includes systemic infections, pronounced blood loss, mechanical ventilator support, multiorgan failure, limitation to volitional intake, and prolonged bed rest.
- Critically ill patients present with a hypermetabolic state, which is marked by increased energy requirements, simultaneous protein synthesis and breakdown, increased lipolysis, and increased insulin resistance.
- There has been a direct link between poor nutritional status and worse hospital outcomes including wound healing, iatrogenic infections, prolonged ventilator dependence, renal insufficiency, and endocrine dysfunction.
- These factors have to be kept in mind while assessing and supporting the patient's nutritional needs. Enteral nutrition refers to the administration of nutrients through the gastrointestinal tract. Parenteral nutrition refers to the intravenous administration of nutrients.

Goals of nutrition in the critically ill

- Caloric requirements during critical illness are increased. If these are unmet by the dietary intake it will lead to a catabolic state with breakdown of a patient's protein and lipid reserves.
- Overfeeding is as harmful as underfeeding as it leads to excess production of CO_2, potentially exacerbating respiratory failure and fatty deposition in the liver and other organs.
- A patient's response to nutritional support is altered by the underlying stress of illness. Care needs to be taken to ensure that metabolic derangements such as hyperglycemia or hypertriglyceridemia are not precipitated or worsened.
- Micronutrients including minerals, vitamins, and trace elements are essential components of nutritional therapy in critically ill patients. Their deficiency can present with systemic disorders.

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Enteral nutrition

- Nutrition provided via the gastrointestinal tract is the preferred route for nutritional support. Its benefits include a more physiologic preparation, less cost, and fewer associated metabolic complications.
- Enteral nutrition allows for preservation of mucosal integrity and stimulation of protective gut functions including immunomodulatory and endocrine effects.
- Enteral nutrition has associated potential risks of aspiration, malabsorption, gut ischemia, and variable tolerance to administered feeds.
- In the absence of contraindications, enteral nutrition should be started within 48–72 hours of ICU admission. Early feeding is associated with lower gut permeability, smaller energy deficits, and concomitant reductions in morbidity and mortality.
- For initiating enteral feeds a temporary enteral access is secured via a nasogastric feeding tube. In patients with anticipated prolonged inability to swallow, a percutaneous endoscopic gastrostomy (PEG) tube can be utilized.
- In patients with gastric distension, poor motility, or concern for aspiration, post pyloric feeding tubes can be used instead of gastric feeding tubes.

Enteral nutrition formulation

- Enteral formulas are premixed solutions with a fixed ratio of non-protein calories to protein. They are designed to provide an energy density of 1–1.5 kcal/mL of solution. The total volume of feed over 24 hours is calculated by dividing the calories required (25 kcal/kg/day) by the energy density of the feeding.
- The protein component in formulary feeds can be either whole protein (soy/casein), peptides, or elemental amino acids depending on the patient's ability to digest and absorp protein.
- The use of supplements such as arginine, glutamine, antioxidants, and omega-3 polyunsaturated fatty acids has been studied with the aim of reducing inflammation and modulating immune response. While animal and in vitro studies have been promising, there is currently inadequate clinical evidence to recommend their widespread adoption.
- Volume loss and hypernatremia can be corrected by supplying free water along with the enteral feeds.

Total parenteral nutrition

- TPN formulations are designed to intravenously provide all necessary macronutrients and micronutrients through one solution. It enables consistent and predictable provision of nutritional intake to the patient.
- Macronutrients include carbohydrates and lipids which serve as the primary source for calories. Protein in the TPN solution is designed to meet the body's requirement for increased synthetic function as well as a source for energy.
- Micronutrients include electrolytes (sodium, potassium, magnesium, calcium, chloride, selenium, chromium), buffers (phosphate, acetate), and other compounds (vitamins, insulin, famotidine).
- The total volume of the formulation is adjusted in accordance with the patient's volume status as well as to meet their daily fluid requirements.
- TPN formulations need to be compounded daily to avoid degradation and microbial contamination.

Indications for TPN

- Diseases of the gastrointestinal system that preclude all enteral feeding for prolonged periods of time:
  - Trauma, bowel perforations, surgical resections, fistulae, and diversions.
  - Inflammatory disorders including severe necrotizing pancreatitis, appendiceal abscess, and gangrenous cholecystitis.
  - Immune disorders including bowel transplant rejection and graft versus host disease.

- Infections including severe *Clostridium difficile* infections, infected peritonitis, and intra-abdominal abscesses.
- Malabsorptive disorders including short gut syndrome and inflammatory bowel disease.
- Neoplastic disorders including obstructive tumor growth, radiation- and chemotherapy-induced mucositis, fistulae, and strictures.
- Vascular disorders including bleeding and ischemic bowel disease.

- Disease conditions that preclude adequate intake of enteral nutrition:
  - Profoundly cachectic patients with poor nutritional reserves.
  - Inability to obtain or maintain enteral access.
  - Enteral nutritional meeting <50% of nutritional requirements.
  - Worsening signs of gastrointestinal tolerance.
- Continuation of ongoing parenteral nutrition.

Energy and macronutrient dosing calculations

- Daily energy requirements are calculated based on the patient's ideal body weight (IBW) (Table. 7.1). Adjusted body weight is used if the patient's weight exceeds IBW by 20%. If the patient's weight is less than 90% of IBW then the actual weight is utilized.
- The estimated daily energy consumption used to determine total energy requirements is 25 kcal/kg/day. In obese patients with a body mass index (BMI) >30, energy requirements are decreased to 22 kcal/kg/day.
- The amount of protein is determined by factors including severity of illness, surgical trauma, and organ system failure (Table 7.2). This allows the protein intake to be matched to the body's synthetic requirements. At the same time, the calories contributed by the proteins are counted towards the total energy requirements, to minimize the risk of overfeeding.
- Half the total caloric requirements are supplied by carbohydrate. The remaining half of caloric requirements is divided between lipids and proteins in a ratio determined by the patient's protein requirement. The amount of each component is calculated using the energy equations (Tables 7.3 and 7.4).

Table 7.1 Determining patients' ideal body weight (IBW).*

Males IBW = 48 kg for the first 5 feet of height + 2.7 kg for each inch taller
Females IBW = 45.5 kg for the first 5 feet of height + 2.2 kg for each inch taller
For patients with actual weight greater than 1.2 times IBW the adjusted body weight (ABW) is used ABW= ([actual weight – IBW] × 0.25) + IBW
For patients with actual weight less than 0.9 times IBW the actual body weight is utilized

* G. J. Hamwi Formula (1964).

Table 7.2 Determining protein requirements (g/day).

Physiologic stress, post-surgery, or wound healing =1.2–2.0 g/kg/day × [weight in kg*]
Critical illness = 1.5 g/kg/day × [weight in kg]
Renal failure, not on renal replacement therapy = 0.8–1.2 g/kg/day × [weight in kg]
Hemodialysis = 1.2–1.4 g/kg/day × [weight in kg]
Continuous veno-venous hemofiltration ≥1.5 g/kg/day × [weight in kg]

* Weight determined from Table 7.1.

Table 7.3 Determining caloric and macronutrient requirements (g/day): carbohydrates.

Total caloric requirement = [weight in kg] × 25 kcal/kg/day
½ × Total caloric requirements = carbohydrates calories ½ × Total caloric requirements = protein + lipid calories
Carbohydrates in grams = carbohydrate calories/calories per gram carbohydrate* = ½ × total caloric requirements/calories per gram carbohydrate = 0.5 × [weight in kg] × 25 kcal/3.4 kcal/g = [weight in kg] × 3.67 g/kg/day

* Carbohydrates = 3.4 kcal/g; lipids = 10 kcal/g; protein = 4 kcal/g.

Table 7.4 Determining caloric and macronutrient requirements (g/day): lipids and proteins.

Lipid calories + protein calories = ½ × total caloric requirements
Protein calories = protein required (from Table 7.2) × calories per gram protein* = 1.5 g/kg/day × [weight in kg] (For critical illness) × 4 kcal/g
Lipids in grams = lipid calories/calories per gram lipid* = [(½ × total caloric requirements) – protein calories]/calories per gram lipid = [(½ × total caloric requirements) – protein calories]/10 kcal/g

* Carbohydrates = 3.4 kcal/g; lipids = 10 kcal/g; protein = 4 kcal/g.

Micronutrients and other additives

- Electrolytes are added to the TPN solution to maintain osmotic and electrolyte homeostasis. Sodium, potassium, magnesium, and calcium are added as either chloride, acetate, or phosphate salts.
- Standard additions include thiamine, folate, multivitamin, and trace elements that include selenium, chromium, copper, and manganese.
- Glycemic control is achieved by adding and titrating the amount of regular insulin in the TPN solution.
- Certain other medications can be added to the TPN solutions depending on their solubility and stability. These include H_2-blockers and heparin.
- A minimum of 150 mL of free water is required for dissolution of the additives in the TPN solution. This can be increased if the patient has additional free water deficits.

Administration

- Parenteral nutrition needs to be infused via a secure central venous access. This avoids complications of phlebitis and injury from extravasation. To minimize infections we recommend maintaining one port dedicated to TPN infusion.
- The total volume of TPN solution is infused at a fixed rate over a 24 hour period. In patients with severe cholestasis or hepatic dysfunction, TPN can be cycled over 12 hours instead.
- While initiating TPN it is important to begin with a half strength solution to minimize complications such as electrolyte derangements, hyperglycemia, and refeeding syndrome. The solution can be advanced over 1–3 days if monitoring panels remain stable.
- While weaning patients off TPN, the caloric strength of the solution should be reduced slowly by 50% before discontinuing the TPN completely.

Adaptation to special situations

- Severe respiratory failure:
  - In patients with respiratory failure or significant ventilator dependence, care should be taken to avoid overfeeding patients. Overfeeding shifts the body into lipid synthesis with concomitant elevation in arterial CO_2 levels potentially lengthening ventilator support duration.

  - For the production of the same amount of energy, the oxidation of lipid generates 25% less CO_2 than carbohydrates. In patients with hypercapneic respiratory failure, a greater proportion of the caloric requirement should be met by lipids.
- Renal failure:
  - Renal failure leads to metabolic acidosis secondary to accumulation of numerous organic acids and increased loss of bicarbonate. TPN orders should be modified to provide additional bicarbonate (as acetate) and to avoid iatrogenic hyperchloremic acidosis.
  - Continuous renal replacement therapies can result in up to 65 g/day loss of protein through the dialysate/ultrafiltrate process. Consequently, it is important to replenish the protein stores at a higher rate (≥1.5 g/kg/day).
  - Volume overload is a common complication of renal failure and has adverse impacts on other organ systems including the heart and the lung. Minimizing the total volume of the TPN solution by concentrating the elements can be helpful in preventing this from arising.
  - Electrolytes need to be carefully monitored in patients to avoid the risk of life-threatening hyperkalemia and other electrolyte imbalances.
- Liver failure:
  - Patients have poor intrinsic synthetic function and may require greater protein replacement.
  - Repletion of micronutrient reserves including water-soluble vitamins requires special consideration.
  - The use of branched chain amino acids in patients with hepatic encephalopathy has yielded mixed results and cannot be recommended as standard practice.
  - If total bilirubin is >4, remove copper and manganese by omitting trace elements to avoid toxicities (these elements are dependent on bile for excretion).

Monitoring

- Daily bedside clinical examination is important to assess vascular access site appearance, volume status, neurologic function, weight monitoring, and readiness for initiation of enteral nutrition.
- Labs include daily monitoring of electrolytes, glucose, liver, and lipid panels.
- For patients on prolonged TPN support, less frequently monitored parameters include TSH, PTH, vitamin D, transthyretin, and carnitine levels.
- 24 hour nitrogen balance has been a validated marker for improved outcomes. It is calculated by subtracting the total nitrogen removed (via urine and stool) from the total nitrogen consumed. Every gram of negative nitrogen balance reflects a loss of 6.25 g of protein or 30 g of muscle mass.
- Indirect calorimetry allows for measurement of resting energy requirements and respiratory quotients (RQs) using measurements of oxygen consumed and carbon dioxide produced. While it requires considerable investment in specialized equipment and training, indirect calorimetry can also provide information on whether there is ongoing over- or underfeeding.
- A RQ of <0.8 signifies a considerable catabolic state where fats and proteins are being utilized as the source of energy. Conversely, in patients with a RQ >1.0 this signifies overfeeding. The goal RQ for patients on TPN is between 0.8 and 1.0.

Complications

- Catheter infections remain the major infectious complication of parenteral nutrition. Common pathogens include *Staphylococcus epidermidis*, *Candida*, and *S. aureus*. For patients on TPN, an established catheter monitoring and maintenance protocol is essential. In patients with suspected infection, replacement of the central catheter at a different site is necessary.
- Hyperglycemia can occur as a result of increased parenteral carbohydrate availability along with concomitant insulin resistance. This can be avoided by gradual titration to the patient's carbohydrate goal as well as regular glucose monitoring. Goal blood glucose should be between 140 and 180 mg/dL.

- Hypertriglyceridemia can occur as a result of lipids infusion, the underlying stress hormone production, and renal insufficiency. In severe cases (triglycerides >1000 mg/dL) this can lead to precipitation of acute pancreatitis. Lipids should be removed from TPN if the plasma triglyceride concentration exceeds 400 mg/dL.
- Hepatic steatosis and cholestasis are known complications of long-term parenteral nutrition. More often seen in children, the exact etiology of fatty liver remains unclear. In the absence of enteral nutrition it is also common for development of cholestasis and biliary sludge. Early resumption of enteral feeding is the definitive treatment. Experimental use of ursodeoxycholic acid and cholecystokinin have shown mixed results.
- Refeeding syndrome can occur when TPN is introduced to patients who are severely malnourished. A rapid intracellular shift of potassium phosphorous and magnesium can precipitate rhabdomyolysis heart failure and cardiac arrhythmias. Careful monitoring and timely replacement of electrolytes can help avoid this complication.
- Intestinal mucosal atrophy can occur in the absence of enteral nutrition. There is risk for bacterial overgrowth and translocation of bacteria in the setting of mucosal denudation and impaired local immunity. The early initiation of trophic feeds helps reduce the risk of infection and translocation. The role of antibiotic agents such as neomycin to inhibit bacterial growth remains poorly defined.

Reading list

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Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 8

Glycemic Control

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OVERALL BOTTOM LINE

- Intravenous insulin is recommended in hyperglycemic patients in the ICU.
- When on intravenous insulin infusion, glucose should be checked every hour until it is at goal for at least 4 hours.
- Once stable, patients on PO diet should be started on long-acting and meal time insulin; patients on continuous feeds should be started on NPH insulin every 6 hours.
- When converting to long-acting insulin, total insulin dose is calculated using the insulin requirement in the last 6 hours of insulin infusion.

Background

- The last decades have witnessed great changes in the definition of glycemic control in the ICU. In the 1990s, stringent glucose control was encouraged. However, later studies have reported the complications of hypoglycemia.
- After the NICE-SUGAR trial demonstrated increased mortality with intensive control, current guidelines recommend a more lenient approach with a target blood glucose level of approximately 140–180 mg/dL. The prevalence of diabetes in the USA has greatly increased to an astonishing 23.9% of the population, 40% of whom are still undiagnosed. The prevalence of diabetes in hospitalized patients appears to be as high as 25%. However, because inpatient diabetes studies are not routinely performed this number is likely underestimated. It is estimated that about 3160 dollars per patient are saved in health care costs as a result of decreased ICU length of stay, sepsis, renal failure, and even mechanical ventilation.
- The causes of hyperglycemia in the ICU are complex and not limited to diabetes but are also caused by the impact of stress hormones such as cortisol including both stress-induced or iatrogenic increases in steroid levels. Differentiation between the causes of hyperglycemia is challenging which is why the exact incidence of each is not yet known.

Pathogenesis

- There is a substantial amount of evidence to suggest that stress-induced hyperglycemia or hospital-related hyperglycemia is an independent risk factor for increased morbidity and mortality when compared with hyperglycemia in diabetic patients.
- Multiple factors contribute to hyperglycemia in the critically ill non-diabetic patient such as stress hormones and inflammatory mediators causing insulin resistance and an increase in the rate of

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gluconeogenesis. Nonetheless, the question that remains unanswered is whether the resultant hyperglycemia is a direct cause of mortality or simply an indicator of the severity of illness.
- The effects of hyperglycemia in the critically ill patient include leukocyte dysfunction, increased oxidative stress, and hypercoagulability and have also been associated with myocardial injury and increase in stroke size.
- Recent evidence has suggested that stress-induced hyperglycemia and hyperglycemia secondary to diabetes do not have the same mortality risk. Stress-induced hyperglycemia is associated with worse outcome, including increased risk of infection and increased length of stay compared with diabetic hyperglycemia.

Risk factors for hyperglycemia

- Diabetes mellitus.
- Medications including exogenous glucocorticoids, vasopressors, lithium, and beta-blockers.
- Inflammatory conditions including sepsis.
- Overfeeding, intravenous dextrose, commonly used parenteral nutrition.
- Dialysis solutions, antibiotic solutions.
- Insufficient insulin.
- Volume depletion can cause hyperglycemia.
- Bed rest.

Prevention of hyperglycemia

In order to potentially reduce the adverse effects of hyperglycemia, it has to be recognized early with the necessary management implemented immediately. However, other than early detection and management, there is no evidence of any means of preventing hyperglycemia prior to its occurrence.

Diagnosis

Differential diagnosis of hyperglycemia in the ICU

Differential diagnosis	Features
Diabetes mellitus	Elevated hemoglobin A1c, weight loss, polyuria, polydipsia
Hormonal disorders such as Cushing's disease or acromegaly	Elevated cortisol/growth hormone, weight gain, Cushingoid features
Drug such as steroids, sympathomimetic drugs	History of medication use

Typical presentation

Critically ill patients with hyperglycemia present differently compared with otherwise healthy diabetic patients. In a critically ill patient, polyuria, polydipsia, and other common symptoms of hyperglycemia may not be present. Patients may present with acute kidney injury and decreased urine output. Due to the severity of illness, including delirium and mechanical ventilation, patients may not be able to communicate their symptoms. Moreover, given the acuity of glucose change, the physical exam may be equivocal and therefore routine blood tests are essential for diagnosis.

Clinical diagnosis

History

Symptoms depend on both glucose level and duration of hyperglycemia:
- Cardiovascular: myocardial injury, electrolyte imbalances causing arrhythmia.
- Constitutional: lethargy.

- Gastrointestinal: nausea, vomiting.
- Neurologic: mental status changes, encephalopathy, seizures, chorea, and other involuntary movements.
- Renal: polyuria, acute kidney injury.

Physical examination

- Depending on the cause of hyperglycemia, some physical exam findings may be present. In stress-induced hyperglycemia, however, arguably the commonest cause in the critically ill patient, the physical exam may not be very revealing.
- Physical exam findings may include acanthosis nigricans in diabetes mellitus and Cushingoid features in Cushing's disease.

Laboratory diagnosis

- Blood gas analyzers are considered accurate, making them the ideal test in the critical care unit. Blood gas analysis requires arterial blood draws, and monitoring via an arterial line would be preferred to provide adequate glucose control. Despite being invasive, it is the consensus recommendation for glucose monitoring of severely ill patients.
- Non-invasive point-of-care (POC) glucose testing devices utilizing fingerstick or tiny amounts of blood obtained via an indwelling vascular line are the most widely used tests for hyperglycemia. These provide rapid results in critically ill patients where glucose fluctuations are unpredictable. POC testing, however, is inaccurate, sometimes differing by as much as 20% from reference values.
- Continuous glucose monitoring systems of the glucose in the interstitial space every 10 seconds is a promising test providing an average glucose value every 5 minutes.
- The glucose trend may be more useful than the absolute glucose value when using less accurate blood glucose monitors such as POC and continuous interstitial glucose monitors.
- Stress-related hyperglycemia in the ICU is acute and therefore would not usually cause an elevation in hemoglobin A1c, making this a method to potentially differentiate between stress-induced hyperglycemia and long-standing diabetes.

Potential pitfalls/common errors made regarding diagnosis of disease

- The diagnosis of diabetes mellitus in the ICU is commonly missed given the incidence of hyperglycemia due to secondary causes. One study showed that 26% of diabetic patients were undiagnosed during their admission to the ICU. These patients had a higher likelihood of requiring an insulin infusion, higher average blood glucose, an increased percentage of hyperglycemia and hypoglycemia (i.e. higher glycemic variability), and increased mortality. These findings suggest that a high suspicion of diabetes in order to anticipate insulin requirement might be beneficial.
- Due to glycemic variability in the critically ill patient, routine monitoring, sometimes continuous, is recommended. A patient who is normoglycemic on admission may not remain so throughout their ICU stay and may even require an insulin infusion at some point depending on the degree of hyperglycemia. Therefore routine glucose measurements are recommended during critical illness with strict guidelines on initiation of insulin therapy.

Treatment

- Much controversy surrounds the idea of what constitutes ideal blood glucose targets in the critically ill patient. Multiple trials have yielded contradictory results. Initially, stringent glucose level control was advocated; however this recommendation was challenged because of the recognition that hyperglycemia was the body's way of adapting to stress. In the early 2000s, the Leuven surgical trial concluded that

intensive glucose control decreased mortality. Despite the faults of this trial, it created a movement for strict glucose goals of around 120 mg/dL.
- However, the subsequent NICE-SUGAR trial, targeting a glucose level less than 180 mg/dL, showed decreased mortality and less hypoglycemia compared with intensive glucose control. Despite the contradicting evidence, the consensus at this time is to target a glucose level of 140–180 mg/dL.
- There is no universally accepted insulin regimen for glycemic control in critically ill patients. However, to avoid prolonged hypoglycemia, which may be harmful, insulin infusions and intermittent short-acting insulin are typically used until the patient is stable enough to be transitioned to subcutaneous insulin.
- No oral agents are used in the ICU for glucose control given the unpredictability of the metabolism in critically ill patients.
- Depending on the glucose level, insulin can be given intravenously or subcutaneously. If there is a reading above 220 mg/dL or two consecutive readings above 180 mg/dL, the intravenous route is preferred. If the glucose reading is between 160 and 179 mg/dL, subcutaneous insulin is given. The options in subcutaneous insulin include short-acting insulin, sliding scale insulin, NPH insulin, and long-acting insulin.

Preferred route of insulin administration

Glucose level (mg/dL)	Route
160–179	Subcutaneous
180–219	Subcutaneous
>220	Intravenous
Two consecutive readings of >180	Intravenous

Monitoring of glucose level

When on intravenous insulin, glucose is checked every hour until it remains within goal for over 4 hours, after which it can be checked every 2 hours. If there is any change in clinical condition, insulin infusion rate, or nutritional support, switching back to hourly glucose checks is advised. When on subcutaneous insulin, glucose can be checked every 2–4 hours initially, then with meals and at bedtime once glucose is within target for over four readings.

Transitioning from intravenous to subcutaneous insulin

- The last 24 hour insulin requirement is calculated by multiplying the requirement in the last 6 hours of insulin infusion, dividing by 6 and multiplying by 20; this will be the total insulin given in a day.
- 40% of the total daily units are given as long-acting insulin and 60% are given as short-acting insulin three times a day.
- If giving NPH insulin, the total dose is divided by 4 and given every 6 hours.
- If a patient is on less than 2 units of insulin per hour while on the drip, consider starting on short-acting insulin.
- Discontinue intravenous insulin 60 minutes after giving subcutaneous insulin.

Nutrition and insulin

- For PO feeds, long-acting insulin and short-acting insulin are preferred.
- For continuous feeds, consider NPH insulin.
- If feeds are held, give basal insulin and hold rapid-acting insulin.
- If continuous feeds are held, hold NPH and long-acting insulin and give short-acting insulin or add D10 at previous rate of feeds.

Management of complications

The commonest complication of glucose control in the ICU is hypoglycemia which is defined as blood glucose less than 80 mg/dL. The association between mortality and glucose level is 'J-shaped' meaning that there is increased mortality at both extremes making it important to avoid hypoglycemia.

- Blood glucose 90–120: hold insulin infusion and repeat blood glucose in 1 hour.
- Blood glucose 71–89: hold insulin infusion and repeat glucose in 30 minutes.
- Blood glucose 51–70: give 12.5 g of 50% dextrose and repeat glucose in 15 minutes.
- Blood glucose <50: give 25 g of 50% dextrose then confirm reading with arterial blood if possible and repeat glucose in 15 minutes.

Treatment/management

See Figure 8.1.

Prognosis

There are clinical, animal, and in vitro studies which support a pathogenic role of acute hyperglycemia by causing immune system dysfunction, coagulation abnormalities, and increasing overall mortality.

Reading list

Finfer S, et al. Clinical review: consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care 2013;17(3):229.

Markovitz LJ, et al. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. Endocrine Pract 2002;8(1):10–18.

Suggested websites

http://resources.aace.com/protocols.html

Guidelines

National society guidelines

Title	Source	Date and weblink
Diabetes Care in the Hospital	American Diabetes Association	2019 https://care.diabetesjournals.org/content/42/Supplement_1/S173
Insulin Infusion Guideline	Society of Critical Care Medicine	2012 https://journals.lww.com/ccmjournal/Fulltext/2012/12000/Guidelines

Evidence

Type of evidence	Title	Comment
Clinical trial	*Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation [NICE-SUGAR] trial*	Significantly higher 90 day mortality in intensive glucose control group compared with moderate glucose control
Clinical trial	*Leuven Surgical Trial*	Intensive glucose control significantly reduced ICU length of stay, hospital length of stay, duration of mechanical ventilation, and acute kidney failure

Images

*** NOT for patients in DKA → follow DKA insulin protocol**

***Consult diabetes team for patients with:**
1) Type 1 diabetes or 2) BG >200 on Algorithm 4

Indications

For critically ill patients in an ICU who meet the following criteria:

- **age ≥14 years**
- **expected ICU length of stay ≥24 hours**
- **IV insulin therapy is consistent with goals of care**
- **≥2 consecutive blood glucoses >180 mg/dL in a 24 hour period**

If **BG 180–219: IV insulin OR standing SQ insulin** (Lispro sliding scale, NPH Q6, lantus) and **check BG Q4 hours**

If **BG ≥220** → **IV insulin**

Initial orders

- ► **Goal BG: 140–180 mg/dL**
- ► Discontinue all prior insulin orders, including sliding scales and oral hypoglycemics
- ► 100 units of regular insulin in 100 mL of normal saline - 1:1 mixture
- ► After each tubing change for insulin drip, prime tubing with insulin solution; waste approximately 20 mL to saturate insulin binding to plastic tubing
- ► IF feeds held for >60 minutes, or no enteral/parenteral feeding – give 3 g of glucose/h with MD order.

  Examples: D5W @ 70 cc/h, D51/2NS @70 cc/h, D10W @ 30cc/h

Monitoring

- ► Blood glucose (BG) – check from arterial or central line when available
- ► Check BG every hour once insulin infusion is started
- ► Once BG is within goal range for ≥4 hours, then can check every 2 hours
- ► **Return to BG hourly checks if:**
  - Any **change in insulin drip rate or BG falls out of range**
  - Any **change in nutritional support** (TPN, PPN, enteral feedings)
    - □ Decrease infusion rate by 50% if nutrition is discontinued or significantly reduced
  - Any **change in clinical condition**, particularly initiation or cessation of:
    - □ **vasopressor requirements**
    - □ **steroid therapy**
    - □ **renal replacement therapy**

HYPOGLYCEMIA PROTOCOL: IF ***BG <70*** - **Note algorithm and hourly rate and discontinue insulin drip**

Initial BG	Action	Monitoring
50–70	Give ½ amp D50 = 25 mL or 12.5 g	Recheck BG in 15 minutes
<50	Give 1 amp D50 = 50 mL or 25 g	Recheck BG in 15 minutes

⇒

Subsequent BG	Action	Monitoring
<60	repeat ½ amp D50 = 25 mL or 12.5 g	Recheck BG in 15 minutes
>120	Resume IV insulin, but move 1 algorithm to the left	Recheck BG in 15 minutes, then hourly

Transitioning from IV insulin – Discontinue the IV insulin infusion 60 minutes after the first dose of SQ insulin is given

- Calculate **24 hour insulin requirements**
- Give approx **1/3 as basal subcutaneous** insulin
  + **Additional 1/3 as short/rapid-acting insulin** in divided doses
- Outpatients not on insulin as output and < 2 units IV insulin/h may before meal only need correction, not basal insulin

- **Enteral nutrition/tube feeds** → if **continuous**, NPH or regular Q6 recommended.
  ↳ if **held**, 1) give basal or correction insulin, 2) hold NPH or regular insulin, 3) D10 @ rate of feeds
- **PO meals: check BG before each meal & bedtime** → Lantus Q24 hours AM +/– rapid acting insulin
  ↳ if **held**, 1) give basal or correction insulin, 2) hold rapid-acting insulin before meal

Initiating the Infusion: **start with Algorithm 1 or Algorithm 2:** ***move up ↑ or down↓ within the same algorithm to adjust the infusion***

MOVE RIGHT – STEP UP insulin infusion:

- If BG >200 AND has not decreased by > 50 mg/dL in 1 hour **OR**
- If BG 180–220, and has not decreased

* ***Most patients start here***

** Starthere for patient requiring ≥80 units insulin/day as outpatient or receiving glucocorticoids

*Algorithm 1	
BG	**Unit/h**
<130	Off
130–139	0.5
140–179	0.5
180–209	1
210–239	1
240–269	1.5
270–299	1.5
300–329	2
330–359	2.5
≥360	4

**Algorithm 2	
BG	**Unit/h**
<130	Off
130–139	1
140–179	2
180–209	2.5
210–239	3
240–269	3.5
270–299	4
300–329	5
330–359	5.5
≥360	7

Algorithm 3	
BG	**Unit/h**
<120	Off
120–129	0.5
130–139	1.5
140–179	3
180–209	3.5
210–239	4
240–269	5.5
270–299	6
300–329	7
330–359	8.5
≥360	10

Algorithm 4	
BG	**Unit/h**
<120	Off
120–129	1
130–139	2
140–179	4
180–209	5.5
210–239	6.5
240–269	8
270–299	10
300–329	12
330–359	14
≥360	15

MOVE LEFT – STEP DOWN insulin infusion:

- If BG decreases by >60 mg/dL in 1 hour **OR**
- If BG is <120 mg/dL

Figure 8.1 Glycemic management in critical care.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 9

Prevention of Complications

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OVERALL BOTTOM LINE
- ICU-related complications can increase morbidity, mortality, and socioeconomic costs of the critically ill patient.
- The occurrence of adverse events related to invasive procedures and medications carries significant consequences particularly in the ICU where these procedures are frequently performed.
- Familiarity with specific complications and their management can help reduce the rate of adverse events.

Neurologic complications

The use of ICU pain assessment tools and daily sedation interruption have led to reduction in ICU length of stay (LOS) and patient mortality rates. The appropriate management of analgesia and sedation (see Chapter 2) can translate into significant improvements in outcome, a shortened duration of mechanical ventilation, a reduced incidence of delirium, and a reduced incidence of significant long-term physical and cognitive dysfunction in ICU survivors.

- Pain, anxiety, agitation, and PTSD have been widely studied in ventilated patients in the ICU. No one sedative agent has been reported to improve the risk of mortality among the critically ill or injured when compared in randomized control trials. For example, propofol may be associated with a shorter time to extubation and recovery from sedation when compared with midazolam. However, the risk of hypertriglyceridemia and hypotension is higher with propofol.
- *Propofol* has also been associated with propofol-related infusion syndrome (PRIS) which includes worsening metabolic acidosis, rhabdomyolysis, hypertriglyceridemia, hypotension, and arrhythmias. Some risk factors for PRIS are:
  - High propofol doses.
  - Prolonged infusion.
  - Liver disease.
  - Use of vasopressors.
  - Underlying mitochondrial disease.
- *Dexmedetomidine* has been linked to a lower risk of drug-associated delirium than alternative sedative agents, but it increases risk of bradycardia and hypotension.
- Only a minority of critically ill patients require deep sedation, for conditions such as severe respiratory failure (e.g. ARDS), intracranial hypertension, and refractory status epilepticus.

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- *Daily sedation interruption and use of sedation scales* to target light sedation have been shown to reduce ventilator time and ultimately LOS. The Richmond Agitation-Sedation Scale (RASS) and Riker Sedation-Agitation Scale (see Chapter 2) have the best reliability and are recommended by clinical practice guidelines.
- *Critical illness polyneuropathy (CIP) and myopathy (CIM)* are major complications of severe critical illness and its management. CIP/CIM affects both motor and sensory axons and, as a consequence, can prolong weaning from mechanical ventilation and physical recovery. Sepsis, systemic inflammatory response syndrome, and multiple organ failure play a crucial role in CIP/CIM. Prevention of risk factors such as high dose steroids, prolonged neuromuscular blockade, prolonged immobility, treatment of the underlying critical illness, and supportive care are the mainstay of treatment. Early mobilization and physical therapy in the ICU have been shown to prevent, as well as aid in treatment of, CIP. Early rehabilitation in the ICU is safe and associated with several benefits, including improvements in muscle strength, functional mobility, quality of life, and reduction in ICU delirium.

Cardiovascular complications

Cardiovascular complications such as myocardial ischemia and cardiac arrhythmias pose an acute and life-threatening risk to ICU patients. Cardiac tachyarrhythmias can arise from a patient's intrinsic cardiac disease, or from medications. Hemodynamic monitoring is essential in the ICU for careful patient management and to determine the etiology of changes in cardiac performance.

- Bedside TTE use has gained popularity since the 1990s and has now become an important instrument in assessing the cause of and appropriate response to most hemodynamic disturbances.
- We recommend the early use of goal-directed bedside TTE in patients with hemodynamic instability, particularly those with increasing need of hemodynamic support to identify underlying treatable causes and help guide fluid resuscitation. Cardiac ultrasound allows intensivists to narrow the differential diagnosis and rapidly diagnose and initiate treatment.
- Cardiac arrhythmias are a commonly encountered problem in the ICU. Preventable factors leading to arrhythmias include electrolyte abnormalities, catecholamine excess, and drug-related adverse effects. Patients should be closely monitored for signs of cardiac ischemia with ECG and cardiac biomarkers. ECG monitoring for QT prolongation with close follow-up can help in avoiding arrhythmias such as torsades de pointes.
- QTc intervals should be particularly monitored in those receiving medications such as procainamide, amiodarone, certain antibiotics (erythromycin, pentamidine, ketoconazole), tricyclic antidepressants, and haloperidol.
- Lastly, electrolyte abnormalities, particularly in hypokalemia, hypocalcemia, and hypomagnesemia, should be aggressively and appropriately repleted to prevent and often treat certain arrhythmias.

Hematologic complications

- *Blood transfusions* are commonly administered to critically ill patients. Previous practices maintained hemoglobin thresholds of >10 g/dL in the critically ill. Recent guidelines based on multicenter randomized control trials indicate that target hemoglobin values of 7–8 g/dL are associated with equivalent or better outcomes in many patient populations and reduce the risk of infection, transfusion reactions and volume overload.
- The 2016 American Association of Blood Banks (AABB) guidelines include the following recommendations for hemodynamically stable patients without active bleeding:
  - Hemoglobin <6 g/dL: transfusion recommended.
  - Hemoglobin 6–7 g/dL: transfusion generally likely to be indicated.
  - Hemoglobin 7–8 g/dL: transfusion may be appropriate in patients undergoing orthopedic surgery or cardiac surgery, and in those with stable cardiovascular disease, after evaluating the patient's clinical status.

    - Hemoglobin 8–10 g/dL: transfusion generally not indicated, but considered for some (e.g. symptomatic anemia, bleeding, acute coronary syndrome with ischemia, and hematology/oncology patients with severe thrombocytopenia who are at risk of bleeding).
    - Hemoglobin >10 g/dL: transfusion generally not indicated except in exceptional circumstances.
- Critically ill patients pose an increased risk of developing venous thromboembolism (VTE) due to their increased length of hospitalization, inactivity, immobilization, and often hypercoagulable states. Mortality associated with deep venous thrombosis is significantly high and often progresses to more serious complications such as pulmonary embolism.
- *Prophylaxis for VTE should be considered in all patients and initiated at the time of admission*. The majority of ICU patients fall under the high risk criteria for developing VTE and pulmonary embolism, particularly those patients who have had an operation or have had major trauma. These patients should be initiated on prophylaxis with low dose unfractionated heparin (5000 U SC every 12 hours) or low molecular weight heparin (enxaparin 40 mg SC every day) as soon as possible, if not contraindicated by bleeding or coagulopathy. Intermittent pneumatic compression devices should be provided to all patients until anticoagulants can be safely initiated.

Gastrointestinal complications

Critical illness is associated with a severe catabolic stress state which contributes to the risk of infections, increased length of hospitalization, and mortality. The Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition now recommend early enteral nutrition initiated between 24 and 48 hours of admission.

- Enteral nutrition increases blood flow to the GI tract, decreases bacterial translocation, improves immune-mediated response in sepsis, and improves overall survival.
- There have been numerous prospective randomized trials performed in the critically ill comparing the effects of enteral versus parenteral nutrition. These trials showed that parenteral nutrition had a higher number of complications associated with infections (particularly pneumonia and central line infections), while enteral nutrition had a significant reduction in hospital LOS, cost of nutrition therapy, and infection rates.
- Critically ill patients have a higher risk of developing stress-related GI lesions due to hypoperfusion of the gastric mucosa, reduction in the protective factors of the mucosa, and increase in gastric acid secretion. These lesions may result in upper GI bleeding which is associated with an increased risk of death in the ICU.
- In a large, prospective, multicenter trial of 2252 ICU patients by Cook et al., the mortality of patients with stress ulcer bleeding was 49% versus 9% in those with stress ulcers, but without an episode of GI bleeding. It also identified mechanical ventilation and coagulopathy as the two main risk factors associated with stress ulcer-related bleeding.
- Acid suppressive medications effectively decrease bleeding rates and are therefore recommended as prophylaxis in high risk patients. Proton pump inhibitors and histamine 2 receptor antagonists have been shown to prevent GI bleeding in the critically ill and are recommended in ICU patients with high risk such as those on mechanical ventilation, or with sepsis or septic shock, coagulopathy, and a history of upper GI bleeding in the past 12 months.
- The routine use of stress ulcer prophylaxis does not reduce overall ICU mortality and therefore the need for stress ulcer prophylaxis should be re-evaluated once the critical period has passed.

Renal complications

- *Hyponatremia* remains one of the most common electrolyte disorders in the critically ill due to both excess fluid administration as well as impaired renal handling of fluids. Hyponatremia is a predictor of increased mortality in congestive heart failure and a marker of severity of illness in the general patient population. Daily monitoring of intravenous fluids and avoiding hypotonic solutions are key in preventing this electrolyte abnormality.

- *Central pontine myelinolysis (CPM)* is an osmolar disruption in the brain that results in non-inflammatory demyelination especially in the pons. CPM is a life-threatening complication of rapid correction of hyponatremia. A conservative approach should be taken to correct hyponatremia by no more than 8 mEq/L over the first 24 hours, and no more than 15–20 mEq/L over 48 hours. Monitoring serum sodium frequently is crucial to the prevention of unrecognized rapid correction; when 3% saline is used, sodium should be monitored every 4 hours.
- *Hyperkalemia* can result from renal insufficiency, rhabdomyolysis, burns, and/or trauma. It is also associated with commonly used medications such as digoxin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, heparin, NSAIDs, and succinylcholine. Treatment of hyperkalemia includes insulin plus dextrose, inhaled high dose beta-agonist; calcium is administered in the setting of electrocardiography changes such as peaked T waves. Sodium polystyrene sulfate is another agent often used for treatment of hyperkalemia, however it should be noted that it has a very slow onset of action and has been linked to a complication of bowel necrosis.
- *Contrast-induced nephropathy (CIN)* is a common cause of hospital-acquired acute kidney injury in the ICU. It leads to prolonged hospital stay, adverse clinical outcomes, and a 5.5% increased overall mortality. Critically ill patients are at a higher risk of developing CIN due to their greater severity of illness and comorbid conditions such as sepsis, hypotension, hypovolemia, and concomitant use of nephrotoxic agents. The mainstays for CIN prevention are hydration (pre- and post-contrast) and the use of low osmolality contrast agents.
  - *N*-acetylcysteine (NAC) has been theorized as a potential agent in preventing CIN. Recent trials have looked at the efficacy of NAC in preventing CIN in the ICU by comparing the incidence of acute renal impairment after administration of iodinated contrast with or without NAC treatment. The results suggest that NAC impedes the rise of serum creatinine but does not improve overall renal function. Additionally, NAC carries a risk of adverse side effects such as anaphylactoid reactions when administered intravenously. Its utility remains questionable and is therefore not recommended for the prevention of CIN.

Procedure-related complications

- Central venous catheterization (see Chapter 3) is a commonly performed procedure in the ICU. Complications vary with site and number of attempts at cannulation. They can be divided between infectious complications and mechanical complications such as arterial puncture, pneumothorax, and atrial/ventricular arrhythmias. Higher rates of infections have been reported with femoral sites versus either subclavian or internal jugular sites while the subclavian site has been associated with difficult to control bleeding.
- Ultrasound-guided catheter placement has shown clear evidence in reducing the rate of the above mentioned mechanical complications. We recommend the use of ultrasound-guided central line placement whenever possible, including wire visualization by ultrasound prior to cannulation. A quick point-of-care ultrasound of the lungs can also be performed post-procedure to assess for a pneumothorax. Telemonitoring should occur throughout the procedure for detection of premature ventricular complexes, particularly while introducing the guidewire and to monitor BP and oxygenation.
- Endotracheal intubation (see Chapter 1) is a commonly performed procedure in the ICU. Circulatory collapse remains the most common and highest risk complication during the peri- and post-intubation period, followed by hypoxia and aspiration. Unlike intubation performed in the operating room by an anesthesiologist, intubation performed in the ICU has not developed specific guidelines. The initial evaluation for any patient requiring airway management should begin with prediction of risk factors that would increase the risk of difficult intubation. The MOCOCHA score (Table 9.1) is a scoring system (>3 of 12 items present suggests higher risk) to predict a difficult airway. We recommend the early use of video-assisted laryngoscopy (GlideScope™) for difficult intubation to avoid multiple attempts, airway trauma, esophageal intubation, and/or prolonged hypoxia.

Table 9.1 MACOCHA score calculation worksheet.

	Points*
Factors related to patient	
Mallampati score III or IV	5
Apnea syndrome (obstructive)	2
Cervical spine reduced mobility	1
Opening mouth <3 cm	1
Factors related to pathology	
Coma	1
Severe **H**ypoxemia (<80%)	1
Factor related to operator	
Non-**A**nesthesiologist	1
Total	12

* Score 0 to 12: 0 = easy airway, 12 = very difficult airway.

- Airway management can be divided into three parts: pre-, peri-, and post-intubation. The pre-intubation period focuses on oxygenation with 100% non-rebreather or non-invasive ventilation such as high flow oxygen, which we prefer over non-invasive bilevel positive pressure ventilation. Complications with BIPAP involve ineffective seal, lung hyperinflation, and introduction of air to the stomach.
  - In patients with GI bleed or those with emesis, we highly recommend nasogastric suctioning while setting up for intubation to remove any gastric residuals and reduce the risk of aspiration. The peri-intubation period focuses on hemodynamic monitoring and anticipation of circulatory collapse with the administration of sedatives. Intravenous fluids should be initiated with standby vasopressor support to maintain mean arterial pressure above 65 mmHg.
  - The post-intubation period should focus on the immediate confirmation of the endotracheal tube with capnography, initiation of appropriate sedatives, and the initial use of lung protective ventilation. The use of point-of-care ultrasound pre- and post-intubation to assess lung sliding can be helpful in confirming adequate endotracheal tube placement and ruling out mainstem intubation while awaiting radiographic confirmation.

Infection control in ICU

Health care-associated infections account for approximately 1.7 million infections and 99 000 deaths annually in the USA. The two most common device-related infections encountered in the ICU are *central line-associated bloodstream infections (CLABSIs)* and *catheter-associated urinary tract infections (CAUTIs)*.

- A CLABSI is a bloodstream infection in a patient with a central venous catheter which cannot be attributed to an infection at any other site. CLABSIs are associated with increased hospital LOS, health care costs, and overall patient mortality. A 2013 meta-analysis of the financial impact of health care-associated infections in the USA found that CLABSIs had the highest financial cost in the health system at $45 814.
- Implementation of prevention bundles and checklists have led to a 46% decrease in CLABSIs from 2008 to 2013. However, there are still an estimated 30 100 CLABSIs per year across the ICU and acute care facilities of the USA. An infection prevention checklist focuses on some of the main methods of CLABSI

prevention including optimal site selection (avoiding femoral access sites), proper hand hygiene, use of chlorhexidine disinfectants, and use of maximal sterile barrier precautions during insertion.

- The use of ultrasound guidance for placement of internal jugular catheter devices has been shown to reduce the risk of CLABSI and other non-infectious complications and should be utilized when possible. Maintenance of these devices is important and may further reduce the rate of infection. Therefore, it is recommended to disinfect catheter hubs prior to access, maintain sterile dry dressing with routine dressing changes, and most importantly to remove the device as soon as it is no longer needed.

- Urinary tract infections (UTIs) are common hospital-acquired infections with an estimated 93 000 UTIs documented in acute care hospitals in 2011 in the USA. UTIs account for approximately 12% of nosocomial infections reported in the ICU. Urinary catheters pose additional risk factors in the elderly such as need for physical restraint, reduced mobility leading to risk of venous thromboembolism, and hematuria.
  - The use of procedure checklists and bundles similar to those utilized for CLABSIs have been shown to decrease the risk of CAUTIs and reduce the inappropriate use of urinary catheters. Hand hygiene and the use of aseptic placement of the urinary catheter are key in reducing the risk of infection. Maintenance of the catheter with a closed drainage system and prompt removal when no longer necessary are equally important in reducing CAUTI rates.
- *Ventilator-associated pneumonia (VAP)* occurs in 9–27% of all intubated patients. The incidence of VAP not only increases the mortality rate but is also associated with increased ventilator days and increased LOS.
  - Prevention strategies including patient positioning, equipment and hand hygiene, and bedside respiratory care (e.g. regular suctioning) have been shown to reduce VAP rates.
  - The use of oral chlorhexidine decreases bacterial colonization of oropharyngeal secretions and therefore the incidence of VAP in those intubated for the short term.

Please also refer to Chapter 44 (Infections Acquired in the Intensive Care Unit).

Reading list

Barr J, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit: executive summary. Am J Health Syst Pharm 2013;70(1):53–8.

Buendgens L, Koch A, Tacke F. Prevention of stress-related ulcer bleeding at the intensive care unit: risks and benefits of stress ulcer prophylaxis. World J Crit Care Med 2016;5(1):57–64.

Carson JL, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA 2016;316(19):2025–35.

Chousterman BG, et al. Prevention of contrast-induced nephropathy by N-acetylcysteine in critically ill patients: different definitions, different results. J Crit Care 2013;5:701–9.

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De Jong A, et al. Early identification of patients at risk for difficult intubation in ICU: development and validation of the MACOCHA score in a multicenter cohort study. Am J Respir Crit Care Med 2013;187:832–9.

Tamma PD, Srinivasan A, Cosgrove SE. Infectious Disease Clinics of North America. Antimicrobial stewardship. Preface. Infect Dis Clin North Am 2014;28(2):xi–xii.

Suggested websites

https://www.cdc.gov/hai/surveillance/progress-report/index.html

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 10

Palliative Care

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OVERALL BOTTOM LINE

- Palliative care plays an important and growing role in quality improvement agendas in many ICUs.
- Early incorporation of palliative care in the ICU has shown favorable results for patient outcomes and family satisfaction regarding end-of-life decision making.
- With the 'baby boomer generation' entering their advanced years, ICUs will continue to experience increasing morbidity, mortality, and socioeconomic constraints.
- Palliative care has to become an integral part of the ICU treatment structure to improve the quality of life in end-of-life care.

Background

- With rapidly expanding populations and advances made in modern medicine, the average life expectancy has shown a steady increase over the last decade. ICUs have seen a surge in the elderly population with life-threatening illnesses but despite modern treatment options ICU mortality remains high.
- It is estimated that approximately 20% of deaths in the USA occur during or shortly after an ICU admission. Of patients who are discharged from the ICU, a sizable population suffers from further physical and neurocognitive symptoms, limiting their quality of life.

Understanding palliative care

- Palliative care in the ICU has shown significant growth in the last decade. With its early integration within the ICU treatment model, it has shown improvement in not only symptom management at the end of life, but also in overall patient and family satisfaction.
- The World Health Organization definition of palliative care emphasizes its most critical role: to prevent and reduce suffering by means of early identification, assessment, and treatment of pain and other problems (e.g. physical, psychosocial).
- Palliative care gained further recognition after a landmark 2010 randomized trial which followed patients with metastatic non-small cell lung cancer with and without initiation of early palliative care. This trial showed that early palliative care led to a significantly improved quality of life and mood. The palliative care arm also found a decrease in aggressive care at the end of life and a longer overall survival period. Although the setting of this trial was carried out in the outpatient and primary care setting it demonstrated the importance of early goal-directed discussion with patients/surrogates regarding their illness with management consistent with their wishes.

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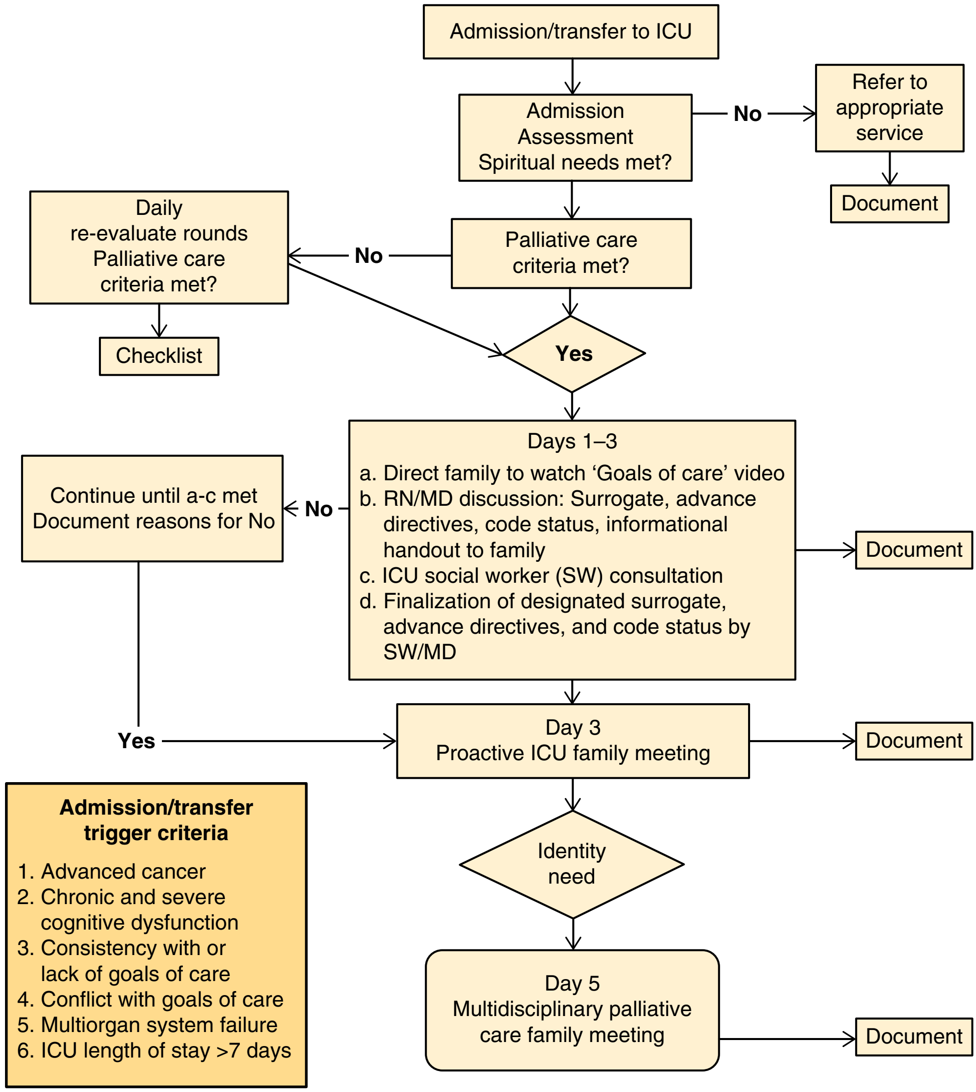
Benefits

- The role of palliative care within the ICU is to assist the patient and family in *making value-based decisions*. Such a model of decision making focuses on establishing goals of care, addressing patient symptoms, and providing family support.
- The palliative consult team is able to provide emotional support and counseling during withdrawal of artificial life-sustaining therapies (that serve to prolong the dying process) and are especially helpful in improving continuity of care in a field that is frequently fragmented.
- Many studies have shown a positive association between palliative care and reduction in ICU length of stay, better utilization of hospital resources, reduction in ICU costs, and ultimately a decrease in the use of potentially inappropriate therapies.
- These studies also found that early communication about patient prognosis and treatment options provided family satisfaction, reduced family anxiety, guilt, and PTSD.

Recommended model of palliative care in the ICU

- Clinical practice guidelines offered by the Center to Advance Palliative Care (CAPC) are one way to apply a standardized method of integrating early palliative care in the management of critically ill patients with advanced illness.
- These clinical practice guidelines follow the standards from the National Quality Forum in its Framework and Preferred Practices for Palliative and Hospice Care, and from the National Consensus Project for Quality Palliative Care. These standards were operationalized by the CAPC with its Improving Palliative Care in the ICU (IPAL-ICU) project.
- The IPAL-ICU model involves hardwiring palliative care into the ICU system, creation of screening criteria to initiation a palliative consult (i.e. advanced malignancy, severe cognitive impairment, multiorgan failure, prolonged ICU hospitalization, conflict or lack of goals of care), guideline formation, and most importantly a set of desired outcome measures.
- The ultimate goal of creating the IPAL-ICU treatment model is to achieve four key points:
  - Timely communication with patient and family.
  - Develop clinical decisions based on patient preference, goals, and values.
  - Provide patient care focusing on providing symptom relief and comfort.
  - Providing family care with open access and ICU support.
- The guideline encourages multidisciplinary rounds as part of the 'integrative model' to occur on a daily basis to gather updates on patients' medical progress while in the ICU and also to screen new potential patients that may benefit from early palliative care. Once a patient has been admitted to the ICU with an expected 5 day or longer course, a screening process should begin to identify palliative care criteria and a discussion should be initiated with patient and family about advance care planning.
- As recommended by the IPAL-ICU algorithm, palliative care communication should begin on ICU day 1 with a focus on establishing a good patient and physician relationship. By ICU days 1–3, the team should have identified an appropriate medical decision maker, discussed acute life-threatening conditions, and investigated advance directive and code status. Information should be provided to the patient and family regarding these matters with the use of educational leaflets and videos.
- While it may be difficult to prognosticate a patient's condition during the first few days of an ICU admission, the goal of the initial meeting is to develop a rapport and to come to an understanding of their current state of health.
- By ICU day 3, there should be an ICU family meeting to address further questions regarding the patient's condition as well as to offer social work and spiritual support. Here it is important to assess if further need for palliative care is present, and an official palliative care consult should be placed accordingly. An official consult would then lead to an interdisciplinary family meeting. Weekly follow-up meetings to further discuss goals of care and the possibility of end-of-life care are recommended (Algorithm 10.1).

Algorithm 10.1 Final workflow incorporating guidelines from the IPAL-ICU project



Devices and withdrawal of artificial life support

- Discontinuation of any medical treatment that is not in line with the patient's goals of care should occur in a thoughtful fashion with consideration given to promoting comfort and reducing anxiety.
- The most commonly performed withdrawal of care within the ICU is the liberation from mechanical ventilation. Though it may seem routine, a well-established protocol can help facilitate a smooth transition for ventilatory withdrawal. Such a protocol should focus on addressing location of ventilator withdrawal, anticipation and treatment of patient symptoms such as pain and dyspnea, and addressing family anxiety.

- Other mechanical life-sustaining devices should also be considered when discussing withdrawal of care. Mechanical circulatory support devices, pacemakers, and defibrillators fall under this category and should be deactivated if a decision is made to withdraw care. Similar to symptom control after ventilator withdrawal, opioids, anxiolytics, and anticholinergic agents should be provided for patient comfort.

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PART 2

Cardiovascular Critical Care

Section Editor: Umesh K. Gidwani

CHAPTER 11

Hemodynamic Monitoring

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OVERALL BOTTOM LINE
- Patients requiring ICU care often require multiple forms of hemodynamic monitoring.
- There has been a tremendous increase in usage of invasive hemodynamic monitoring in order to enhance our understanding of patients' hemodynamics and helping to guide appropriate therapeutic interventions.
- Although there is a paucity of evidence to support the use of many of these invasive monitors, they are very commonly used in the ICU.

Arterial lines

Indications

- Direct arterial pressure monitoring is recommended for all ICU patients with hemodynamic instability who require inotropic or vasopressor medications as well as significant ventilatory deficits. This allows for continuous monitoring of blood pressure as well as access to the arterial circulation for the measurement of arterial oxygenation and frequent blood sampling.
- As the pulse moves peripherally, the pressure waveform is distorted with higher systolic pressure and pulse pressure (Figure 11.1).

Locations for placement

- Radial artery: common site of cannulation. Check collateral flow of ulnar artery with the Allen's test, which has low reliability.
- Brachial artery: located in antecubital fossa, lack of collateral circulation, median nerve injury possible.
- Axillary artery: can cause axillary nerve damage from hematoma or traumatic cannulation.
- Femoral artery: prone to pseudoaneuryms and atheroma formation.
- Dorsalis pedis and posterior tibial arteries: most distorted waveforms.

Contraindications

- Deficiencies of collateral circulation (e.g. Raynaud's phenomenon).

Complications

- Rates of up to 10%.
- Hematoma, bleeding, vasospasm, arterial thrombus, aneurysm, dissection, pseudoaneurysm, infection.

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Advanced arterial hemodynamic monitoring

- Multiple proprietary systems have developed algorithms for estimating cardiac output from the arterial waveform. Arterial pulse contour analysis can evaluate stroke volume to calculate cardiac output and examine stroke volume variation to assess fluid responsiveness.
- Characteristics of the arterial pressure waveform are affected by changes in vascular compliance, aortic impedance, and peripheral arterial resistance, limiting the accuracy and utility of this class of monitors.

Pulse contour analysis

The principle is based on the hypothesis that stroke volume is proportional to the area under the curve of the systolic segment of an arterial waveform.

PiCCO system (Pulsion Medical Systems)

- Pulse contour cardiac output (PiCCO) requires the insertion of a central venous catheter and a thermodilution arterial line.
- It provides hemodynamic monitoring by combining pulse contour analysis and a transpulmonary thermodilution technique to provide a continuous display of PiCCO cardiac index (L/min/m^2) and stroke volume (mL/kg).
- Calibration of the PiCCO to more accurate transpulmonary thermodilution cardiac output measurements needs to be repeated every 8 hours, or more frequently if the patient is hemodynamically unstable.
- Additional data derived from the PiCCO system include:
  - Extravascular lung water index (mL/kg).
  - Global end-diastolic volume (measure of cardiac preload in mL/m^2).
  - Systemic vascular resistance index (dyn·s/cm^5/m^2).
  - Stroke volume variation (%).

FloTrac™ system (Edwards Lifesciences)

- Requires an arterial line.
- Uses pulse contour analysis based on an algorithm to provide continuous cardiac output, stroke volume, and stroke volume variation in real time.
- Provides an estimate of cardiac output using the standard deviation of the arterial pulse pressure around the mean arterial pressure and a conversion factor.
- Calibration is not required.

Pulse power analysis

LiDCO system

- Lithium dilution cardiac output (LiDCO) requires a peripheral or central arterial line.
- Uses pulse power analysis rather than pulse contour analysis. The algorithm is based on the assumption that the net power change in the system in a heartbeat is the difference between the amount of blood entering the system, the stroke volume, and the amount of blood flowing out peripherally.
- Requires calibration using transpulmonary lithium indicator dilution technique via a peripheral venous line. It is not as accurate when the patient is receiving lithium or certain neuromuscular-blocking agents.

Central lines

- CVP is measured via a central line at the level of the right atrium or vena cava. It is equal to the right ventricular end-diastolic pressure.
- CVP can be used to determine preload, the filling pressure of the heart. It has been used to estimate whether a patient is adequately resuscitated as well as helping to assess right ventricular function.

Table 11.1 Waveform components.

Waveform/ descent	Phase of cardiac cycle	ECG	Mechanical event
A wave	End diastole	Follows P wave	Pressure increase due to atrial contraction
C wave	Early systole	Follows R wave	Pressure increase due to tricuspid bulging into the right atrium
V wave	Late systole	End of T wave	Pressure increase due to systolic filling of the atrium
X descent	Mid systole		Drop in atrial pressure due to atrial relaxation
Y descent	Early diastole		Drop in atrial pressure due to early ventricular filling

- A central line allows for infusion of hypertonic solutions and medications that can damage peripheral veins. It also allows for serial venous blood analysis and venous blood gas (VBG).
- Of particular importance, lactate and central venous saturation measurements from VBGs have been used to direct resuscitation efforts.
- Normal CVP is 2–8 mmHg.

Common locations

- Internal jugular, subclavian vein, femoral vein.

Complications

- Rates of up to 15%.
- Inadvertent arterial puncture and/or cannulation, pneumothorax, hemothorax, cardiac arrhythmias, venous air embolism, infections.

Waveform components

As the heart beats, a CVP waveform is produced. There are three waves and two descents (Table 11.1 and Figure 11.2).

Controversy regarding the utility of CVP monitoring

- Use of CVP to guide fluid management has been heavily debated. CVP is not useful as a static measurement. Trending the CVP can be useful to determine a patient's response to a fluid challenge.
- Useful measurements depend on proper calibration, normal pulmonary resistance, and right heart function.

Pulmonary artery catheter monitoring

Background

- Swan and Ganz first described the pulmonary artery catheter (PAC) in 1970 and it was widely used in the 1980s. However, as more trials were published in the 1990s and 2000s, its popularity declined.
- Connors et al. published a prospective randomized trial in 1996 finding an increased cost, length of stay, and mortality in critically ill patients with a PAC.
- The Fluid and Catheter Treatment Trial compared mortality, ventilator-free days, and ICU length of stay among patients with acute lung injury and found no significant benefit to PAC in PAC-directed resuscitation. The use of PAC resulted in no difference in LOS in the ICU or mortality.

Procedure

The PAC requires placement of a balloon-tipped catheter into the right atrium, across the tricuspid valve, into the right ventricle, and across the pulmonary valve, until it is 'wedged' into a pulmonary artery. At each anatomic location different pressure waveform profiles will be seen (Figure 11.3).

Indications

- Acute MI with progressive hypotension or suspected mechanical complications.
- Acute right ventricular failure.
- Intraoperative/perioperative care:
  - Vascular surgery.
  - Cardiac surgery.
  - Moderate/high risk patients receiving goal-directed resuscitation.
- Undifferentiated shock.

Direct measurements

- Right atrial pressure (0–8 mmHg).
- Right ventricular pressure (systolic 20–30, diastolic 0–5 mmHg).
- Pulmonary artery pressure (systolic 20–30, diastolic 8–12 mmHg).

Indirect measurements

- Pulmonary artery wedge pressure (PAWP): surrogate for left ventricular preload (4–12 mmHg).
- Cardiac output (CO)/cardiac index: measured using the thermodilution technique (reliability of measurement is affected by tricuspid or pulmonary regurgitation or intracardiac shunts):
  - Normal CO: 4–8 L/min.
  - Normal CI: 2.5–4 L/min/m^2.

Calculated measurements

- Stroke volume (SV) = CO/HR:
  - Normal: 60–120 mL/beat.
- Systemic vascular resistance (SVR) = 80 × [(MAP – RAP)/CO]:
  - Normal: 1600–3000 dyn·s/cm^5.
- Pulmonary vascular resistance (PVR) = 80 × [(mean PAP – mean PAWP)/CO]:
  - Normal: 37–250 dyn·s/cm^5.

Complications

- Rates of 5–10%.
- Bleeding, hematoma, arterial puncture/cannulation, pneumothorax, hemothorax, tachyarrhythmias, right bundle branch block, complete heart block, pulmonary artery rupture, myocardial perforation, infection.

Echocardiography

Ultrasound echocardiography is an operator-dependent hemodynamic assessment, which is a quick and non-invasive measurement tool. Its effectiveness has not yet been proven in randomized clinical trials.

Cardiac function and anatomy can be assessed using five standard views (Table 11.2).

- Stroke volume can be estimated with echocardiography:
  - SV = $\pi \times R^2 \times$ velocity time interval (VTI) of the left ventricular outflow tract (LVOT) (R= radius of LVOT in cm).

- Parasternal long axis view is used to measure diameter of the LVOT.
- Apical five chamber view is used to measure the VTI with pulsed Doppler.

- Routine measurements of the size of the IVC and collapsibility with respiration can be used to estimate right atrial pressure (RAP) and fluid responsiveness in patients via the subcostal view on echocardiography.
  - Size ≤2.1 cm, collapses >50% during inspiration = RAP 0–5 mmHg.
  - Size >2.1 cm, collapses >50% during inspiration = RAP 5–10 mmHg.
  - Size >2.1 cm, collapses <50% during inspiration = RAP 10–20 mmHg.

Table 11.2 Echocardiography views.

View	Findings
Parasternal long axis	Pericardial effusion, LV/RV size and function, septal kinetics
Parasternal short axis	Pericardial effusion, LV/RV size and function, septal kinetics
Apical four chamber	Pericardial effusion, LV/RV size and function
Subcostal four chamber	LV/RV size and function, preferred view in cardiac arrest
Inferior vena cava longitudinal view	Determine preload sensitivity

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Images

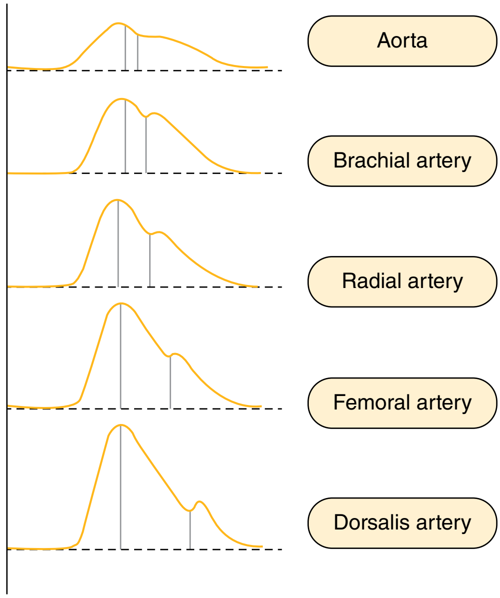

Figure 11.1 Arterial pressure waveforms at different locations in the vascular tree.

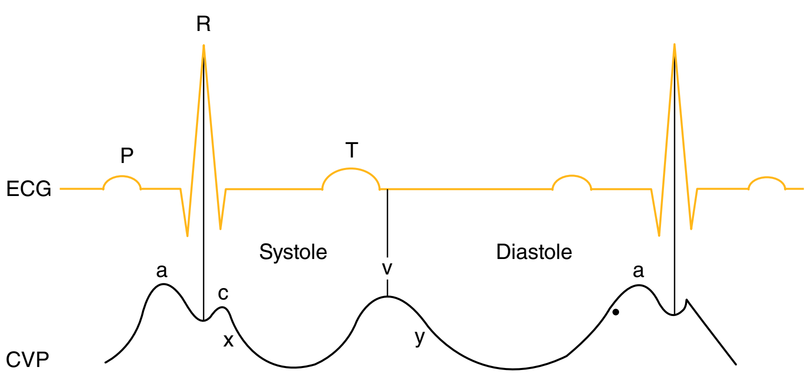

Figure 11.2 Components of the CVP waveform throughout the cardiac cycle.

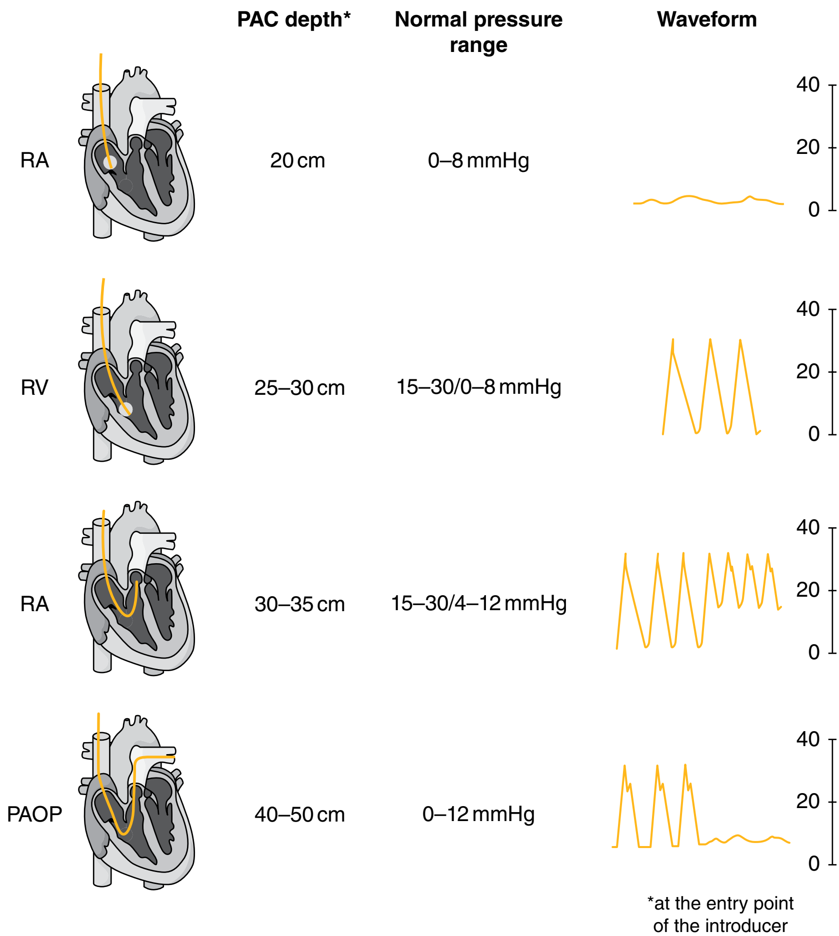

Figure 11.3 Placement of a pulmonary artery catheter. At different depths of catheter placement different waveform profiles will be identified.

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CHAPTER 12

Vasoactive Drugs

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OVERALL BOTTOM LINE

- Verify the patient's blood pressure yourself.
- Think about central access early to facilitate vasopressor and fluid administration.
- It is critical to tailor clinical management to each individual patient and shock physiology. Understand *why* your patient is hypotensive.
- Think about pH and volume status. Vasoactive agents will only have limited effect if these parameters are not corrected.
- Appropriate monitoring including continuous telemetry is important. Many of these agents cause ventricular arrhythmias.
- Vasoactive drugs may not be enough. Pay close attention and appreciate the appropriate timing for additional hemodynamic monitoring or mechanical circulatory support.

Physiology

- The purpose of vasoactive drugs in the ICU is to improve the mean arterial pressure (MAP) and cardiac output (CO) by affecting left ventricular contractility, volume status, and systemic vascular resistance (SVR). Vasopressors are generally indicated in the setting of circulatory shock. MAP is related to CO and SVR by the equation:

$$\text{MAP} \approx \text{CO} \times \text{SVR}$$

- Cardiac output is the volume of blood the heart is able to pump through the circulatory system per minute. The resistance to blood flow due to the entire systemic vasculature is known as the systemic vascular resistance, and is primarily a function of vascular smooth muscle tone. CO is directly related to heart rate (HR) and stroke volume (SV) as seen by the equation:

$$\text{CO} = \text{HR} \times \text{SV}$$

- Stroke volume is a function of left ventricular end-diastolic filling pressure (preload), the resistance against which the ventricle has to eject blood during systole (afterload), and the intrinsic ability of the cardiac muscle to contract (contractility). Each of these hemodynamic factors needs to be interrogated to find the reason for circulatory shock, and will be critical in understanding how to tailor therapy to the patient's physiology.

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Basic properties

- Vasopressors are agents that increase blood pressure by causing vasoconstriction (SVR) through the activation of various receptor targets.
- Inotropes are agents that augment stroke volume, and thus cardiac output, by increasing myocardial contractility.
- Inodilators are agents with inotropic properties, but also with vasodilatory effects.
- It is important to note that some vasoactive agents have mixed actions, as they can exert effects on multiple receptor targets.

Indications

- Vasopressors and inotropes are typically used in the ICU to support the blood pressure during circulatory shock and improve end-organ perfusion.
- Vasodilators and venodilators are used to lower SVR and blood pressure, or to reduce filling of the heart.

Types of shock

- There are four different types of shock: cardiogenic, distributive, hypovolemic, and obstructive. Mixed forms of shock can also occur.
- Table 12.1 shows the typical hemodynamic changes seen with each type of shock, but individual clinical situations often involve more complicated physiologic determinations.

Table 12.1 Different forms of shock states.

	Cardiac output	Heart rate	Stroke volume	Systemic vascular resistance	Venous pressure (PCWP/CVP)
Cardiogenic	↓	↑	↓	↑	↑
Distributive (i.e. sepsis, anaphylaxis, neurogenic shock)	↑ (occasionally impaired)	↑	↑ (occasionally decreased)	↓	Normal or ↓
Hypovolemic	↓	↑	↓	↑	↓
Obstructive (i.e. pulmonary embolus, pericardial tamponade, tension pneumothorax)	↓	↑	↓	↑	Normal or ↓ (increased in pericardial tamponade)
Mixed	↓↑	↑	↓↑	↓↑	↓↑

Selecting vasoactive therapy

It is critical to understand the physiology of the shock that you are treating, and the receptor targets for each vasoactive medication, so that you can tailor therapy to the particular clinical situation.

Low preload (LVEDP)

- In distributive, obstructive, or hypovolemic shock, proper fluid resuscitation is critical to improving blood pressure, cardiac output, and end-organ perfusion. Monitoring of hemodynamic parameters and filling pressures can be helpful in this setting.
- In mixed shock states, invasive hemodynamic monitoring can be useful in determining the predominant mechanism of shock and to customize therapy to the physiology of the patient.

Receptors affected by vasoactive medications

- Vasoactive medications often work as agonists or antagonists of adrenergic or parasympathetic receptors. These selected receptors represent the principal targets for vasoactive therapy in the intensive care setting (Table 12.2).

Key principles of vasoactive medication use

- Diagnose and understand mechanism causing hypotension:
  - Physical examination, urine output, laboratory testing, imaging, and invasive hemodynamic monitoring can be important tools to differentiate the nature of the patient's shock.
  - Dosage and selection of medication should be titrated to achieve a blood pressure sufficient to maintain end-organ perfusion, as evidenced by metrics such as mentation, urine output, and blood lactate levels.
  - Critically ill patients also require frequent re-evaluation for further hemodynamic insults, response to therapy, or side effects that may require changes in therapeutic strategy.

Table 12.2 Action of vasoactive medications.

Receptor	Location	Action
α-1 adrenergic	Vascular smooth muscle (peripheral, renal, coronary)	Systemic vasoconstriction – increased SVR
α-2 adrenergic	Vascular smooth muscle and central nervous system	Vasodilation – decreased SVR Sedation
β-1 adrenergic	Cardiac muscle	Increased heart rate (chronotropy) and contractility (inotropy) Increased cardiac output Minimal vasoconstriction
β-2 adrenergic	Vascular smooth muscle (peripheral and renal)	Vasodilation Reduced SVR
Dopamine (D_1)	Vascular smooth muscle (peripheral, renal, splanchnic, coronary, cerebral)	Vasodilation in capillary beds
Acetylcholine (ACh)	Parasympathetic nervous system (heart, sinoatrial and atrioventricular nodes, GI tract, eyes)	Has chronotropic effects on heart Atropine is an antagonist of muscarinic ACh receptors Atropine can stimulate or accelerate AV node conduction
Phosphodiesterase 3 (PDE-3)	Cardiac muscle and vascular smooth muscle	Increased contractility (inotropy) and improves diastolic relaxation (lusitropy) Vasodilation
Vasopressin (V_1, V_2)	Vascular smooth muscle and renal collecting duct	V_1 – stimulation causes vasoconstriction V_2 – mediate water reabsorption in renal collecting system

- Tailor vasoactive therapy to correct the specific hemodynamic derangements underlying the hypotension:
  - This requires understanding adrenergic receptors and mechanisms of action.
  - An example of this principle is the use of a pure alpha-adrenergic agonist such as phenylephrine for hypotension resulting from cardiogenic shock. It might seem intuitive to use such a drug to improve hypotension from inadequately contracting the left ventricle. However, understanding the effect of such a drug on the hemodynamic equations noted above will allow you to conclude that phenylephrine use would be counterproductive. It would lead to decreased stroke volume from an increased afterload on the weakened left ventricle without the benefit of inotropic support.
- Most vasoactive drugs act on multiple receptors, and many agents activate different receptors depending on the dose administered:
  - The best example of this is dopamine, which preferentially stimulates β-1 receptors at low doses and α receptors at higher doses.
  - Similarly, dobutamine can increase myocardial contractility by stimulating β-1 receptors. However, it can cause vasodilation by simultaneous activation of β-2 receptors.
  - The principle is to understand that vasoactive medications can have mixed hemodynamic effects, and often have different responses based on dose.
- A given vasoactive agent can have both direct actions and reflex actions:
  - The vascular system is closely regulated by multiple physiologic mechanisms including the autonomic nervous system that seeks to ensure cardiovascular stability.
  - For example, phenylephrine-induced vasoconstriction can lead to increased mean arterial pressure, which may lead to baroreceptor activation and a compensatory reflex bradycardia.
- Responsiveness to the vasoactive medications can decrease over time due to a phenomenon known as tachyphylaxis:
  - Up-titration of doses or initiation of new agents with different receptor targets must be done regularly.
- Central line access and arterial line monitoring are a must:
  - Catecholamines and vasopressor agents are given as continuous infusions due to their short half-lives. They carry significant risks of peripheral extremity ischemia due to potent vasoconstriction as well as skin necrosis if they extravasate. Central venous access is usually necessary.
  - With all intravenous vasoactive infusions, invasive hemodynamic monitoring with an arterial line is needed because of rapid hemodynamic changes and side effects such as arrhythmias

Vasoactive medications in focus

Epinephrine	
Receptor binding	α-1, β-1, β-2
Pharmacology	β receptor predominant at lower doses, α receptor predominant at higher doses
Dosing range	0.01–0.10 μg/kg/min (for 70 kg adult, that is 0.7–7 μg/min)
Clinical scenarios to consider use	Cardiac arrest Extreme hemodynamic collapse Additional agent when already on several vasopressors Shock after cardiac surgery Right ventricular failure Anaphylaxis
Clinical pearls	Reserved for refractory or severe shock despite multiple vasopressors or extreme hemodynamic compromise Associated with decreased mesenteric, coronary, and renal blood flow and regional ischemia resulting in a lactic acidosis

Norepinephrine	
Receptor binding	α-1, β-1, β-2
Pharmacology	Less β receptor activity than epinephrine α receptor predominant at higher doses
Dosing range	0.01–3 μg/kg/min (for 70 kg adult, that is 0.7–210 μg/min)
Clinical scenarios to consider use	Septic shock (first line) Cardiogenic shock (first line) Vasoplegia after cardiac surgery
Clinical pearls	If norepinephrine requirements are increasing, evaluate volume status and pH Norepinephrine has been demonstrated to be equivalent to other vasopressor agents, including dopamine, with less adverse events, including tachyarrhythmias In cardiogenic shock, mortality was lower with norepinephrine than with dopamine. This has led to use of norepinephrine as first line agent for cardiogenic shock, including shock from an acute myocardial infarction The Surviving Sepsis Campaign guidelines recommend norepinephrine as the first line agent for septic shock

Dopamine	
Receptor binding	α-1, β-1, β-2, D1
Pharmacology	Binds DA receptors at low doses, promoting vasodilation particularly in the splanchnic circulation Binds adrenergic receptors at higher doses, leading to vasoconstriction
Dosing range	0.5–3 μg/kg/min, predominantly D_1 agonism 3–10 μg/kg/min, weak β-1 agonism; promotes norepinephrine release >10 μg/kg/min, increasing α-1 receptor agonism: • Vasodilation of capillary beds (low dose) • Increased contractility and chronotropy (medium dose) • Vasoconstriction (high dose)
Clinical scenarios to consider use	Cardiogenic shock complicating acute myocardial infarction with moderate hypotension (SBP 70–100 mmHg); however, this has largely been replaced by norepinephrine Symptomatic bradycardia (temporizing measure)
Clinical pearls	While often used as a vasopressor agent that can be used peripherally while central access is being set up, extravasation of dopamine is not benign Renal dosing of dopamine for acute kidney injury was hypothesized to be of use due to vasodilation and improved blood flow to the splanchnic circulation at lower doses (1–3 μg/kg). However, clinical trials have not shown a benefit and it is currently not recommended for this use

Dobutamine	
Receptor binding	β-1, β-2, minor α-1
Pharmacology	Synthetic catecholamine with preferential β-1 agonism (3:1 ratio of β-1 to β-2), inotropic effect β-2 activity causes vasodilation, which makes dobutamine an inodilator Progressive α-1 agonism at high doses causes vasoconstriction
Dosing range	2–40 μg/kg/min Dose in ICU for cardiogenic shock rarely exceeds 10 μg/kg/min
Clinical scenarios to consider use	Acute decompensated systolic heart failure Refractory septic shock associated with low cardiac output (also known as 'hypodynamic' or 'cold' sepsis, a relatively small subset of patients) Pharmacologic stress testing (e.g. for ischemia, viability, aortic stenosis severity)

(*Continued*)

Dobutamine	
Clinical pearls	Tolerance develops after a few days of therapy Ventricular arrhythmias can occur at any dose Dobutamine significantly increases myocardial oxygen demand so do not use in patients with acute coronary syndromes, severe and unstable coronary disease, or ongoing ischemia Dobutamine has inotropic properties that increase myocardial contractility and cardiac output, while the vasodilatory effects further improve cardiac output by reducing afterload. This makes dobutamine an ideal agent in decompensated heart failure. Remember to use an agent such as norepinephrine as the initial agent if shock and hypotension are present

Milrinone	
Receptor binding	PDE-3
Pharmacology	PDE-3 inhibitor PDE-3 inhibition increases intracellular cAMP concentrations, enhancing contractility and promoting vascular smooth muscle relaxation Relatively long half-life (2–4 hours) Renal elimination
Dosing range	0.125–0.75 μg/kg/min (renal adjust)
Clinical scenarios to consider use	Acute decompensated systolic heart failure Right ventricular failure
Clinical pearls	Fewer arrhythmogenic and chronotropic side effects compared with catecholamines, but vasodilatory effects can worsen hypotension that limits the use of milrinone in patients with shock Can be useful if adrenergic receptors are downregulated or desensitized in setting of chronic heart failure, or after chronic β-agonist administration Potent pulmonary vasodilator so can be useful in right ventricular (RV) failure by lowering pulmonary vascular resistance (RV afterload) Long half-life (2–4 hours); hypotension can persist for longer so short-term infusions may be more beneficial than continuous infusions

Phenylephrine	
Receptor binding	α-1
Pharmacology	Pure α-1 agonism Minimal inotropic and chronotropic effect Rapid onset, short half-life
Dosing range	0.4–9.1 μg/kg/min (for 70 kg adult, that is 28–637 μg/min) Bolus administration possible, usually 0.1–0.5 mg every 5–15 minutes
Clinical scenarios to consider it	Dynamic intracavitary gradient: 'suicide ventricle' after transcatheter aortic valve replacement (TAVR), anteroapical STEMI, hypertrophic cardiomyopathy with systolic anterior motion of the mitral valve and LV outflow obstruction, and Takotsubo cardiomyopathy Inadvertent combination of sildenafil and nitrates Hypotension during PCI or anesthesia-related hypotension Hypotension in the setting of atrial fibrillation with rapid ventricular rate Aortic stenosis with hypotension Vagally mediated hypotension during percutaneous diagnostic or therapeutic procedures
Clincial pearls	Phenylephrine increases MAP by raising SVR (afterload), and therefore is particularly useful when SVR <700 dyn·s/cm^5 Increased afterload can result in decreased stroke volume and cardiac output in patients with pre-existing cardiac dysfunction

(*Continued*)

(*Continued*)

Phenylephrine	
	Contraindicated in patients with SVR >1200 dyn·s/cm^5, which is most patients with cardiogenic shock Lower concentration (20 μg/mL) available which can be infused peripherally while awaiting central line placement Generally not recommended for septic shock unless serious arrhythmias happen with norepinephrine Can cause reflex bradycardia

Vasopressin	
Receptor binding	V1, V2
Pharmacology	Agonism of V1 receptors on smooth muscle causes vasoconstriction Agonism of V2 receptors in nephron induces translocation of aquaporin water channels to plasma membrane of collecting duct cells
Dosing range	Fixed dose: 0.04 units/min
Clinical scenarios to consider it	When avoiding β agonism is desired (e.g. left ventricular outflow obstruction, tachyarrhythmia) or when trying to reduce dose of first line agent Hypotension accompanied by severe acidosis Second line agent in refractory vasodilatory/septic shock
Clinical pearls	Vasoconstrictive effect is relatively preserved despite conditions of hypoxia and acidosis (which can attenuate effects of catecholamines) Doses above 0.04 units/min have been associated with coronary and mesenteric ischemia and skin necrosis Rebound hypotension often occurs after withdrawal of vasopressin. To avoid this, the dose is slowly tapered by 0.01 units/min every 30 minutes

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with website

CHAPTER 13

Mechanical Circulatory Support

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OVERALL BOTTOM LINE

- Circulatory support can be provided by mechanical means when pharmacologic therapies prove insufficient.
- These devices may be used to stabilize a patient with the goal of recovery of pump failure or as a bridge to a decision regarding further care.

Overview of devices and indications

Mechanical circulatory support can be classified in terms of the duration of intended support.

Short-term mechanical circulatory support

- These devices are used in patients with cardiogenic shock refractory to pharmacologic therapies.
- They are typically used for days, rather than weeks.
- Examples include:
  - Intra-aortic balloon pump (IABP).
  - Impella® devices.
  - Extracorporeal membrane oxygenation (ECMO).

Intermediate-term mechanical circulatory support

- These devices are robust extracorporeal pumps that can be used for several weeks.
- They are usually employed emergently and serve as bridge to transplant or bridge to decision (BTD).
- Examples include:
  - TandemHeart® device.
  - CentriMag™ device.

Durable (long-term) mechanical circulatory support

- These devices are indicated in patients with NYHA stage IV progressive heart failure unresponsive to medical therapies.
- Examples include:
  - Left ventricular assist device (LVAD): indicated for predominant LV failure as bridge to transplant or destination therapy.
  - Total artificial heart (TAH): indicated for biventricular failure as bridge to transplant.

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Short-term mechanical circulatory support devices

Intra-aortic balloon pump

- While the IABP has been a mainstay in the management of cardiogenic shock, current evidence has cast doubt as to the efficacy of the IABP in cardiogenic shock. Larger studies are underway.
- The IABP consists of an elongated polyurethane balloon (35–40 mL) inserted percutaneously through the femoral artery. A pump is attached to the balloon that uses helium to inflate the balloon during diastole (closure of the aortic valve), and to deflate the balloon during systole (opening of the aortic valve).
- Ideal location: the balloon tip should be at the level of the carina (Figure 13.1), and the distal balloon end should lie above the renal arteries. If prolonged support is required, can consider axillary insertion to allow sitting upright and possible ambulation.

Indications

- Cardiogenic shock complicating acute ST elevation MI (ACC/AHA stage IIa/b).
- Refractory unstable angina.
- Mechanical complications of acute MI (papillary muscle rupture leading to mitral regurgitation (MR) or ventricular septal defect (VSD)).
- Support of high risk coronary intervention (such as percutaneous coronary intervention, coronary artery bypass graft).
- Refractory heart failure as a bridge to further therapy.
- Intractable ventricular arrhythmia as a bridge to further therapy.
- Intractable MI awaiting further therapy.

Contraindications

- Moderate or severe aortic insufficiency.
- Aortic dissection.
- Aortic aneurysm.
- Occlusion/severe stenosis of distal aorta.

Postulated mechanisms of action

- Increased (augmented) diastolic pressure → improved coronary perfusion → increased myocardial oxygen delivery.
- Increased mean arterial pressure (increased diastolic, decreased systolic) → improved systemic blood flow.
- Decreased afterload: deflation of the balloon creates a suction effect causing decreased end-distolic blood pressure → reduced aortic pressure at the start of systolic ejection → decreased afterload → increased stroke volume, decreased myocardial oxygen demand, and improved systemic perfusion.

IABP pressure waveform

- Unassisted wave: the wave immediately before balloon inflation (Figure 13.2).
- Augmented wave: waveform that correlates with balloon inflation.
- Assisted wave: the wave immediately following the augmented wave is called the assisted wave (seen in 1:2 or higher ratios). Due to balloon inflation, the assisted end-diastolic pressure is lower, thereby reducing afterload and 'assisting' ventricular contraction.

Complications

- Vascular complications during insertion or removal.
- Limb ischemia (3–20%).
- Balloon rupture (rare): indicated by blood in connecting tube. Managed by placing patient in Trendelenburg position and immediately removing balloon.
- Hemolysis and consumptive thrombocytopenia.
- Catheter-related infection.

Impella intraluminal catheter-based axial flow pump

- The Impella is a catheter-based device that propels blood by a non-pulsatile axial flow Archimedes-screw pump.
- Once the Impella catheter is confirmed to be in the desired position, it is connected to an external controller system where the user can adjust the rotational speed to provide the desired flow rate.

Left ventricular Impella

- The Impella originally was designed to provide LV support.
- It is inserted into the femoral artery either percutaneously or surgically by femoral cut-down and is advanced in a retrograde fashion so that the tip housing the pump sits in the left ventricle (Figure 13.3A).
- The pump pulls blood from the left ventricle through an inlet area near the tip and expels blood from the catheter into the ascending aorta distal to the aortic valve.
- The three available models displace increasing amounts of blood with progressively larger axial motor sizes:
  - Impella 2.5: catheter diameter 9 Fr, 12 Fr pump motor, flow rate up to 2.5 L/min.
  - Impella CP: catheter diameter 9 Fr, 14 Fr pump motor, flow rate up to 4.3 L/min.
  - Impella 5.0/LD: catheter diameter 9 Fr, 21 Fr pump motor, flow rate up to 5 L/min.

Right ventricular Impella

- The Impella RP is designed to provide RV support; it comes in one size and provides flow rates greater than 4.0 L/min.
- The Impella RP is inserted via the femoral vein, into the right atrium, across the tricuspid and pulmonic valves, and into the pulmonary artery (Figure 13.3B).
- The motor which sits in the terminal IVC propels blood through the catheter and to the outlet opening near the tip of the catheter in the main pulmonary artery.

Indications

- During high risk percutaneous coronary intervention in hemodynamically stable patients with severe coronary artery disease.
- Treatment of cardiogenic shock occurring after myocardial infarction or open heart surgery.
- Impella RP is indicated for right heart failure refractory to conventional therapy.

Extracorporeal membrane oxygenation

- ECMO provides cardiopulmonary support similar to the cardiopulmonary bypass circuit used in cardiac surgery.
- Blood is drained from the vascular system, circulated outside of the body by a mechanical pump, oxygenated, and then reinfused into the circulation (Figure 13.4).
- There are two primary types of ECMO: veno-venous (V-V) and veno-arterial (V-A):
  - V-V ECMO helps only with oxygenation by oxygenating *venous* blood and returning it back to the *venous* circulation.
  - V-A ECMO provides both oxygenation and circulatory support. *Venous* blood is oxygenated and returned back into the *arterial* circulation, thereby bypassing both the lung and heart.
- Venous access is usually by cannulation of the internal jugular vein or femoral vein, while arterial access is through the femoral artery.

- Cannulas are inserted primarily by cardiothoracic surgeons at the bedside, catheterization lab, or operating room.
- An ECMO team is required, including a cardiologist, cardiothoracic surgeon, intensive care nurse, and perfusionist (specially trained respiratory therapist).

Indications

ECMO is deployed when conventional therapies have failed, risk of mortality is imminent, and the disease process is either reversible or there is a plan to bridge to VAD or organ transplant.

Indications for V-V ECMO

- Acute respiratory distress syndrome.
- Provide lung rest in airway obstruction, pulmonary contusion, or smoke inhalation.
- Primary graft failure after lung transplantation.
- Bridge to lung transplant.
- Lung hyperinflation due to status asthmaticus.
- Pulmonary hemorrhage or massive hemoptysis.

Indications for V-A ECMO

- Cardiogenic shock.
- Inability to wean from cardiopulmonary bypass after cardiac surgery.
- Primary graft failure after heart or heart–lung transplantation.
- Chronic cardiomyopathy as a bridge to VAD or heart transplantation.
- Peri-procedural support for high risk percutaneous cardiac interventions.

Contraindications and complications

Device	Contraindications	Complications
All devices	Severe peripheral vascular disease Irreversible neurologic disease	Bleeding Vascular injury Infection Neurologic injury
Impella LP/CP	Moderate to severe aortic insufficiency Moderate to severe aortic stenosis Left ventricular thrombus Recent stroke Aortic abnormalities Contraindication to anticoagulation	Hemolysis Pump migration Aortic valve injury Tamponade due to LV perforation Aortic insufficiency Ventricular arrhythmia
Impella RP	Disorders of pulmonary artery wall precluding placement Severe stenosis or regurgitation of tricuspid or pulmonary valve Thrombus in the right atrium or vena cava Contraindication to anticoagulation	Hemolysis Pump migration Tricuspid/pulmonic valve injury Tamponade due to RV perforation Tricuspid/pulmonic insufficiency Ventricular arrhythmia
ECMO	Severe aortic insufficiency Unwitnessed cardiac arrest Disseminated malignancy Not LVAD, heart, or lung transplant candidate Contraindication to anticoagulation	Thrombosis of circuit Upper body hypoxia due to incomplete retrograde oxygenation LV dilation Systemic gas embolism

Intermediate-term mechanical circulatory support devices

TandemHeart

- The TandemHeart utilizes an extracorporeal continuous flow centrifugal pump that withdraws oxygenated blood from the left atrium and pumps it into the arterial circulation (Figure 13.5).
- One cannula is inserted into the femoral vein and another into the femoral artery.
- The left atrium is accessed through the venous system by trans-septal puncture.
- Provides up to 4 L/min of blood flow.
- There are no randomized controlled data on the TandemHeart, which limits its more widespread use.

Indications

- Cardiogenic shock.
- Extracorporeal circulatory support for procedures lasting up to 6 hours and not requiring complete cardiopulmonary bypass (e.g. mitral valve reoperation, valvuloplasty, surgery of the vena cava).

CentriMag

- The CentriMag is a surgically implanted extracorporeal centrifugal pump that utilizes a magnetic rotor (Figure 13.6). It can provide support to either ventricle or both.
- For RV support, the cannulas are placed in the right atrium and pulmonary artery to bypass the right ventricle.
- For LV support, the cannulas are placed in the left atrium and aorta to bypass the left ventricle.
- It is possible to insert two CentriMag devices to provide biventricular support (as shown in Figure 13.6).
- Provides up to 10 L/min of blood flow.

Indications

- Cardiogenic shock with acute RV failure, approved for use for up to 30 days.
- Acute LV failure, approved for use for up to 6 hours while longer term options are considered.

Contraindications and complications

Device	Contraindications	Complications
CentriMag	Contraindication to anticoagulation	Thromboembolic events Air embolism
TandemHeart	Ventricular septal defect Moderate to severe aortic insufficiency Contraindication to anticoagulation	Cannula migration Tamponade due to perforation Thromboembolism Air embolism during cannula insertion Interatrial shunt development

Durable (long-term) mechanical circulatory support devices

Left ventricular assist device

- A LVAD is a mechanical pump that works in parallel with the patient's heart, used in the management of end-stage cardiac failure that is refractory to advanced medical therapy.

Evolution of LVAD devices

- Historically, LVADs can be divided into first, second, and third generation devices.
- The first generation devices provided pulsatile flow and were bulky, noisy, and associated with high complication rates. However, they were evolutionary and led to the first continuous flow devices.
- The second generation devices were smaller and had an axial flow rotor powered by a battery connected to a small caliber driveline.
- The Thoratec HeartMate™ XVE and HeartMate II devices are in wide use in the USA and other countries. Blood flows through an inflow cannula from the apex of the left ventricle to the pump and returns back through an outflow cannula to the ascending aorta.
  - The landmark REMATCH study (2001) demonstrated significant survival benefit in patients with end-stage heart failure treated with a pulsatile HeartMate XVE LVAD versus optimal medical therapy (52% versus 25% survival at 1 year, $P = 0.002$) with an improved quality of life.
- Third generation devices are centrifugal pumps that are designed for long durability, compact size, and optimization of blood flow through the device to minimize the risk of thrombus formation and hemolysis.
  - The HeartWare™ HVAD is a continuous flow centrifugal pump with the Impeller partly magnetically suspended and with no bearings.
  - The Thoratec HeartMate III is a magnetically levitated centrifugal flow pump designed to minimize the risk of pump thrombosis.
  - In the MOMENTUM trial (2018) comparing the HeartMate III with an axial flow pump in 366 patients with advanced heart failure, the centrifugal flow pump was superior to the axial flow pump with regard to the composite primary outcome (2 years free of disabling stroke or survival free of reoperation to replace or remove a malfunctioning device). Mortality rates and disabling stroke rates were similar in the two treatment groups.

Components

The LVAD receives blood from the left ventricle and returns it to the ascending aorta (Figure 13.7), with Figures 13.8 and 13.9 showing details of some of the components.

Indications

- Bridge to cardiac transplant.
- Destination therapy as long-term assistance for patients who are ineligible for transplant (approximately 40% of implants).
- Bridge to recovery for potential reversible myocardial pathology.

Management of cardiac arrest in patients on mechanical circulatory support

- Step 1: call the VAD attending or fellow.
- Step 2: establish an arterial line. The most important step is establishing an accurate blood pressure with an arterial line.
- Step 3: begin chest compressions. While chest compressions run the risk of cannula dislodgment, it should be performed in cases where the mean arterial pressure is 0 (patient has actually lost perfusion, as opposed to situations with poor perfusion where an alternative means to restore this may be considered).
- Step 4: consider volume bolus and inotropes where appropriate.

Parameters used to monitor LVAD function

Parameter	Definition	Range	Increase	Decrease
Flow	Calculated value (estimated from power and speed) Directly proportional to power ↑Power = ↑ flow estimate ↓Power = ↓ flow estimate	4–6 L/min	Abnormal increase in power may lead to a falsely elevated flow, i.e. increased drag on rotor due to pump thrombosis results in high power requirements and falsely elevated flow reading	
Power	Directly measured by system controller	HW: 4–6 watts HMII: 5–8 watts	High power (trend is more important than transient spikes) may be due to development of thrombus.	Obstruction of outflow graft (kinking, stenosis, aortic anastomosis)
Speed	Speed is set by medical team Individualized for each patient based on echo optimization, as well as clinical markers including BP and symptoms	HW: 2600–3200 rpm HMII: 8600–9600 rpm	Pump programmed to avoid potential suction events by reducing speed	
Pulsatility index (PI) (displayed on HMII only)	Correlates with degree of native LV residual contractility (max flow – min flow/mean flow)	3–6	Increased LV contractility – exercise, ionotropes, myocardial recovery (rare): • Increased preload • Volume overload	Decreased LV contractility: • Underfilling of LV • Inflow/outflow obstruction

HMII, HeartMate II; HW, HeartWare.

LVAD troubleshooting

	Pulsatility index	Power	Flow	Fixed speed
HeartMate II	3–6	5–8 watt	4–6 L/min	8600–9600 rpm
HeartWare	N/A	4–6 watt	4–6 L/min	2600–3200 rpm
	Pump logistics	**Echo findings**	**Diagnostic aids**	**Management options**
Right ventricular failure	Lower pulsatility Lower flow Possible suction events	RV dilation and dysfunction Septal bowing to right	Right heart catheterization (RHC)	Diuretics Inotropes Digoxin Pulmonary vasodilators Echo optimization Temporary percutaneous support: Impella RP device, or right-sided TandemHeart

(*Continued*)

(*Continued*)

	Pump logistics	Echo findings	Diagnostic aids	Management options
Hypovolemia	Lower pulsatility Suction events Lower flow	Decompressed LV	Response to fluid challenge Hypotension Orthostatic vital signs	Intravenous fluid
Tamponade	Lower flow Lower pulsatility Suction events	Effusion or localized peri-RV clot Clear tamponade physiology rarely seen with VAD support	Exam RHC CT scan Hypotension	Pericardial drainage/ surgical exploration
Pump thrombus	Higher power Higher flow estimation (falsely elevated) Lower pulsatility	Ramped speed study Decreased LV unloading Dilated LV Aortic vein (AoV) opening Increased mitral regurgitation (MR)	Hemolysis labs Log file anlaysis RHC Device auscultation ('running rough') LV angiography	Increased anticoagulation Inotropic support if in heart failure Thrombolysis (high risk of bleeding) Pump exchange surgery
Volume overload	Higher pulsatility (occasional)	RV dysfunction, tricuspid regurgitation Dilated LV • AoV opening • Increased MR	Physical exam: volume overload, jugular venous pressure, rales RHC	
Hypertension	Possible higher pulsatility (especially on VAD)	Non-specific	Doppler blood pressure	Antihypertensive therapy
Pump or percutaneous lead failure	Not maintaining set speed VAD running irregular Controller alarms	Dilated LV Poor LV unloading Increased MR AoV opening	Device auscultation Log file analysis X-ray of percutaneous lead	Percutaneous lead repair LVAD surgical replacement
Inflow/ outflow obstruction	Higher/ lower power Higher/ lower pulsatility Higher/ lower flow	Ramped speed study Dilated LV Poor LV unloading AoV opening Increased MR	CT angiography CXR Fluoroscopy LV angiography Hemolysis labs	Stenting of outflow graft obstruction Pump replacement

LVAD-related complications

Complication	Details	Etiology/ presentation	Investigations	Treatment considerations
Bleeding	GI bleeding (20% within 1 year) Epistaxis	AC related Acquired von Willebrand factor deficiency GI angiodysplasias and arteriovenous malfunctions	Colonoscopy and/ or endoscopy If no source, consider tagged RBC scan	Hold AC and antiplatelets for hemodynamically significant bleeding Possible reversal of AC if INR elevated and clinically unstable bleed Monitor device parameters closely while holding AC

(*Continued*)

Complication	Details	Etiology/ presentation	Investigations	Treatment considerations
CVA (10% within 1 year)	Hemorrhagic (5% within 1 year) Thromboembolic (5% within 1 year)	Presents with new focal neurolgic deficit, altered mental status Pump thrombosis	CTA head/neck Evaluate for signs of pump thrombosis CTA of LVAD	Neurosurgery and neurology consultation Possible discontinuation/ reversal of AC in the setting of intracranial bleed Possible use of mechanical thrombectomy for large vessel occlusion
Device thrombosis	Subtherapeutic INR Hypercoaguable state	May present with power spikes, high flow alarms, cardioembolic events, pigment nephropathy, cola colored urine Heart failure symptoms	Trend daily LDH (3× upper limit of normal) Plasma-free Hb Urinalysis: hemoglobinuria Echo RAMP study CTA of LVAD	AC protocols: bivalirudin, heparin Thrombolysis in select cases Surgical VAD exchange Inotropic support in heart failure IVF with diuresis if evidence of hemglobinuria
Infection (includes device-related infection such as infectious endocarditis, mediastinitis, bacteremia)	Driveline infection Pocket infection	Fevers/chills, etc. Discharge and/or pain from driveline site	Microbiology Driveline site C/S, blood culture, Imaging: CT chest and abdomen scan for deep infection	ID consult Appropriate antibiotics Occasionally surgical debridement

Total artificial heart

- A TAH is a durable mechanical circulatory support device that is used for patients with severe biventricular dysfunction or other structural abnormalities that make them poor candidates for LVAD implantation.
- Surgical implantation includes sternotomy, removal of both native ventricles and their associated atrioventricular valves, and implantation of the TAH by connecting each synthetic ventricle to the respective atria and great vessel.
- The TAH is connected to an external power source via a driveline similar to an LVAD.
- The device is composed of two polyurethane pneumatically powered ventricles, each with a single leaflet tilting disc valve.
- The most commonly used TAH device is the CardioWest™ TAH (Syncardia).

Indications

- CardioWest is approved as a bridge to transplant device in transplant eligible patients at risk of imminent death from biventricular failure.

Complications

- Surgical implantation complications most commonly include infection (72%), bleeding (42%), hepatic dysfunction (36%), and respiratory dysfunction (30%).
- Long-term complications include driveline failure, systemic or driveline infections, thromboembolic events, and bleeding.

Reading list

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Images

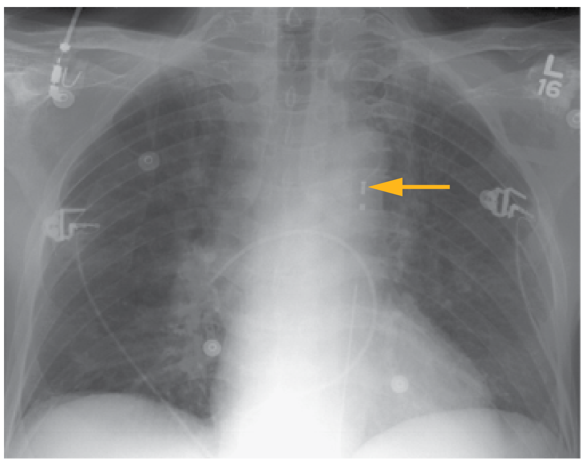

Figure 13.1 CXR demonstrating the tip of the IABP in the correct position (arrow).

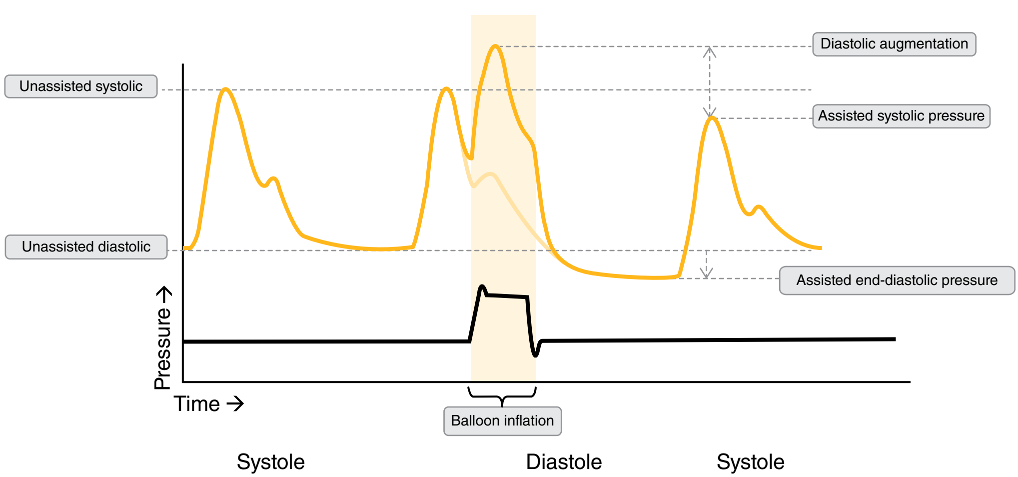

Figure 13.2 Normal IABP pressure waveform.

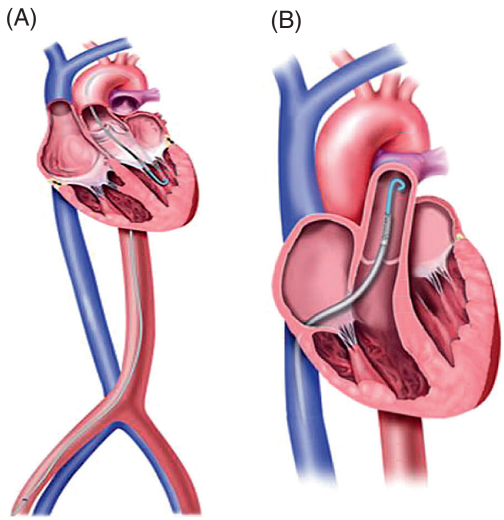

Figure 13.3 (A) Left heart catheterization. Using femoral arterial access, the catheter has been guided into the left ventricle. (B) Right heart Impella inserted via the femoral vein.

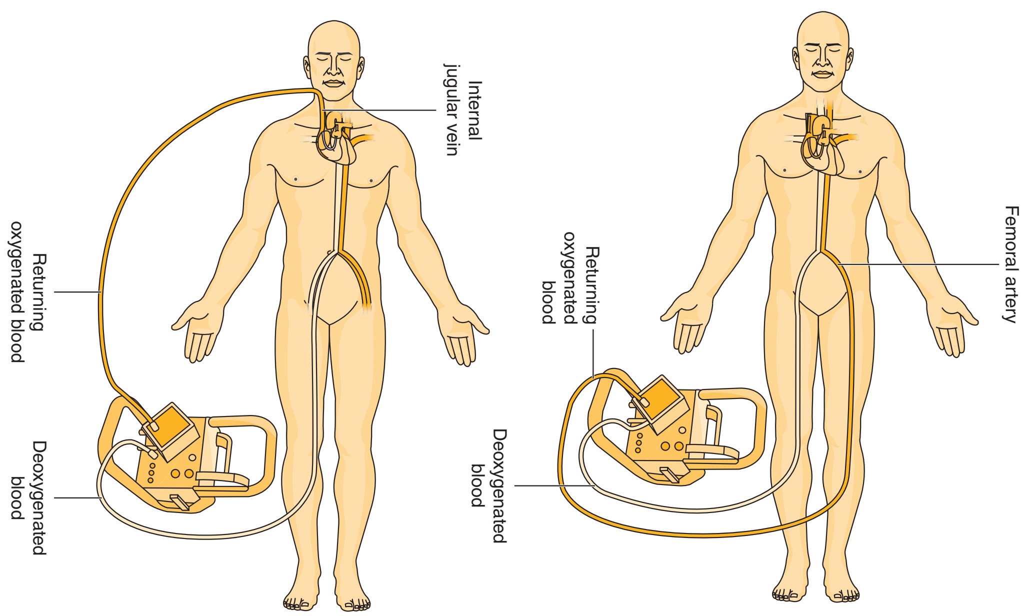

Figure 13.4 Veno-venous and veno-arterial ECMO circuits.

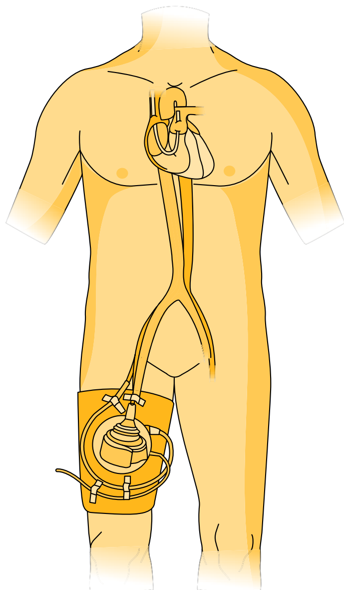

Figure 13.5 TandemHeart assisting the left ventricle in pumping oxygenated blood.

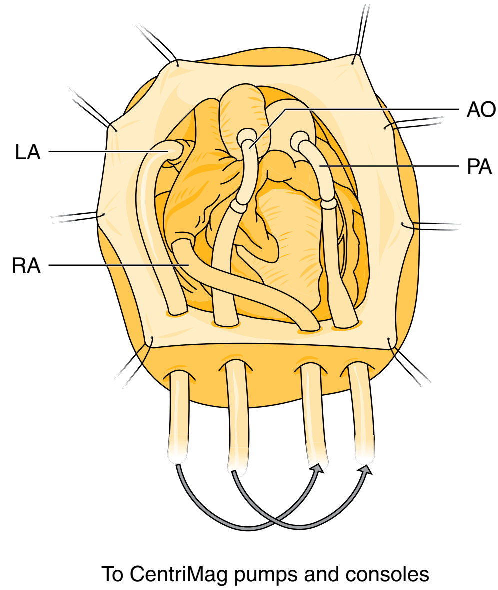

Figure 13.6 CentriMag extracorporeal pump.

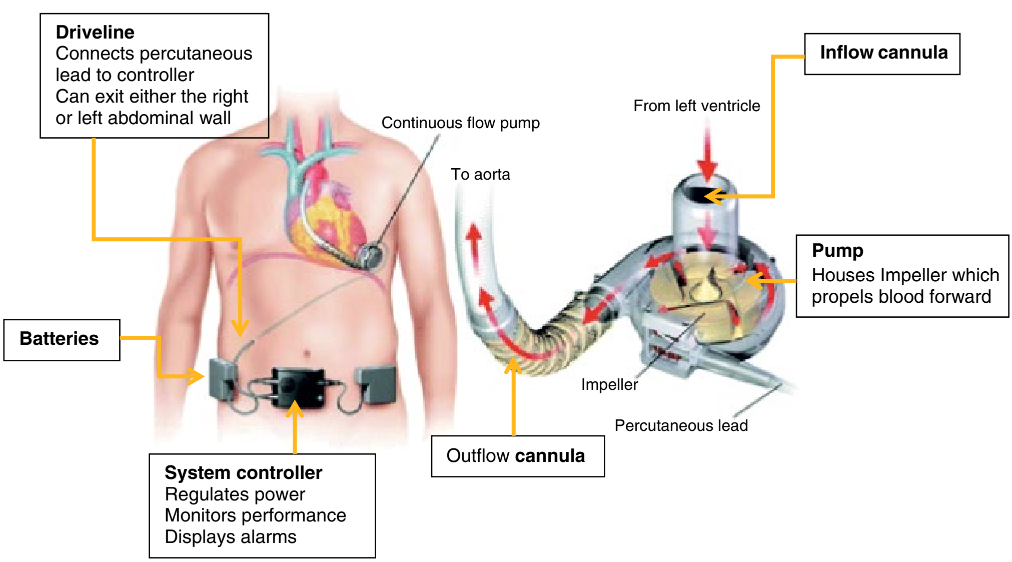

Figure 13.7 LVAD components.

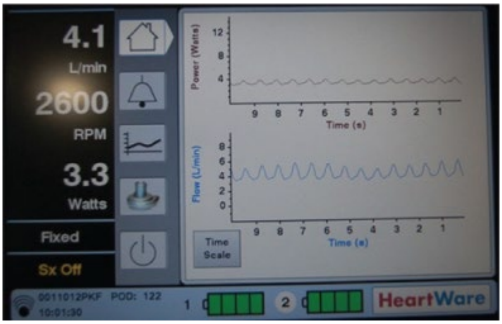

Figure 13.8 HeartWare controller screen.

Figure 13.9 HeartMate II controller screen.

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This includes multiple choice questions.

CHAPTER 14

Acute Hypertensive and Aortic Syndromes

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OVERALL BOTTOM LINE

- Hypertensive emergency is a common event which can result in aortic dissection.
- Type A (ascending) aortic dissection is managed surgically.
- Type B (descending) aortic dissection is managed with blood pressure control.

Background

- Hypertensive urgency is defined as severely elevated blood pressure >220 systolic or >120 diastolic.
- Hypertensive emergency is defined as severely elevated blood pressure with signs of end-organ damage.
- In the cardiac critical care setting, hypertensive emergency can manifest as aortic dissection.

Incidence/prevalence

- Hypertensive emergency of any kind is common with approximately 1–5% of those who have hypertension experiencing a hypertensive emergency over their lifetime.
- Incidence of aortic dissection is estimated at 30 cases per million individuals per year.

Etiology

- Chronic hypertension predisposes to both hypertensive emergency and aortic dissection.
- Several conditions can predispose to aortic dissection including Marfan's syndrome, vasculitis, syphilis, and Turner's syndrome.

Pathology/pathogenesis

- Blood enters the media layer of the aorta and forces apart the intimal layer and creates a false lumen which can lead to aortic rupture, hemopericardium, or ischemic injury to any end organ dependent on flow from the affected region of the aorta (Figure 14.1).

Predictive/risk factors

- Hypertension.
- Genetic/congenital aortic disease.
- Atherosclerosis.
- Trauma.
- Cocaine use.
- Inflammatory/infectious diseases of the aorta.
- Pregnancy.

Prevention

- Weight reduction, diet modification, avoidance of smoking, and control of cholesterol may prevent hypertension and aortic disease.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Screening

- The US Preventive Services Task Force (USPSTF) suggests adults over 40 years have their blood pressure checked annually; those between 18 and 39 checked annually in the setting of risk factors; those without risk factors and with no known history of hypertension should be checked every 3 years.
- The USPSTF suggests males between 65 and 75 years who have a history of smoking should have a one-time screening for abdominal aortic aneurysm by ultrasonography.

Secondary prevention

- Adherence to an antihypertensive regimen and regular medical follow-up can prevent a second hypertensive emergency or aortic emergency.

Diagnosis

- Acute pain is the most common clinical history: pain can occur in the chest, back, or abdomen depending on the location of dissection; dissection in the absence of chest pain is rare.
- On exam there may be a pulse deficit or a difference in blood pressure (>20 mmHg) in both arms in the presence of dissection; an aortic murmur may be present if the tear involves the aortic valve; a focal neurologic deficit may be present.
- A D-dimer of <500 ng/mL is highly predictive for excluding dissection.
- CXR may show a widened mediastinum. TEE or MRA are useful in a patient who may not be able to tolerate contrast or safely be transported to the CT scanner. The imaging modality of choice is a CT angiogram (Figure 14.2).

Differential diagnosis of aortic dissection

Differential diagnosis	Features
Acute coronary syndrome	Usually gradual onset of chest pain described as tightness or pressure rather than tearing or radiation to the back
Esophageal rupture	Usually preceded by vomiting or an esophageal procedure and will present with concurrent sepsis May have mediastinal crunch
Pulmonary embolism	Pleuritic chest pain often accompanied by tachycardia and hypoxia in the presence of a clear CXR
Pneumothorax	Sudden onset chest pain with absent or decreased breath sounds on one side Subcutaneous emphysema may be present
Pericardial tamponade	Shortness of breath with pleuritic chest pain Easily identified on bedside transthoracic echocardiogram ECG will often show diffuse ST elevations rather than focal

Typical presentation

- Aortic dissection typically presents with abrupt onset pain, the location of which may vary depending on the location of the dissection.
- The pain may be described as a ripping or tearing, but often is just described as sharp.
- The pain is often severe and may be associated with hemodynamic instability or other signs and symptoms due to lack of end-organ perfusion depending on the location of the dissection.

Clinical diagnosis

- A description of the pain is important in diagnosing aortic dissection. Abrupt onset is typical for dissection. It can be in the chest but may also be in the back or abdomen depending on the location. It can be associated with syncope, neurologic symptoms, or signs of heart failure.

Physical examination

- There may be a pulse deficit in the carotid, brachial, or femoral artery depending on the location of the dissection.
- There may be a significant difference in blood pressure on both arms.
- A heart murmur may be found if there is associated aortic regurgitation, which is a diastolic decrescendo murmur; this occurs in half to one-third of ascending dissections.
- A neurologic deficit may be found depending on the location of the dissection.

Laboratory diagnosis

List of diagnostic tests

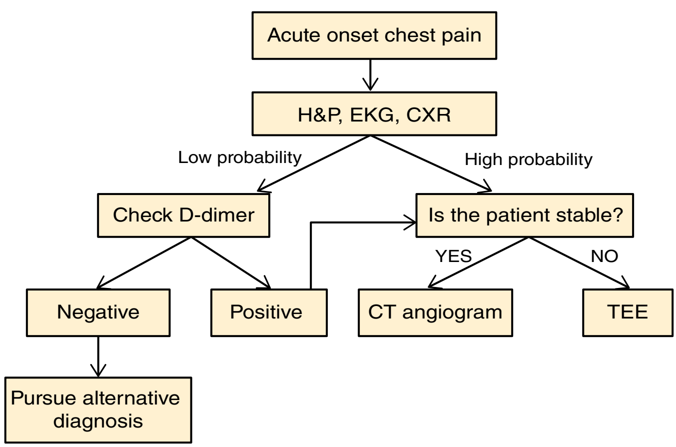
- D-dimer: useful in excluding dissection if the value is lower than 500 ng/mL.
- Multiple experimental tests have been studied (soluble elastic fragments, smooth muscle myosin heavy chain, C-reactive protein, fibrinogen, fibrillin fragments) but none are validated.

List of imaging techniques

- CT angiogram: preferred test in a hemodynamically stable patient.
- MRA can be considered in the hemodynamically stable patient with chronic kidney disease.
- Echocardiogram: TEE is a quick test that can evaluate for ascending dissection and is ideal in the unstable patient.
- CXR: should be used as a screening imaging study in all patients with chest pain and any concern for dissection.

Diagnostic algorithm (Algorithm 14.1)

Algorithm 14.1 Diagnostic approach to a patient with chest pain and suspected aortic dissection



Potential pitfalls/common errors made regarding diagnosis of disease

- In a patient presenting with chest pain, the discovery of a pericardial effusion or acute coronary syndrome, especially in the RCA distribution, does not exclude the possibility of a concurrent aortic dissection.
- Aortic dissection can present without pain in 6–10% of patients.

Treatment

Treatment rationale

- Ascending dissection is a surgical emergency.
- Descending dissection can be treated medically with blood pressure control in most patients.

Table of treatment

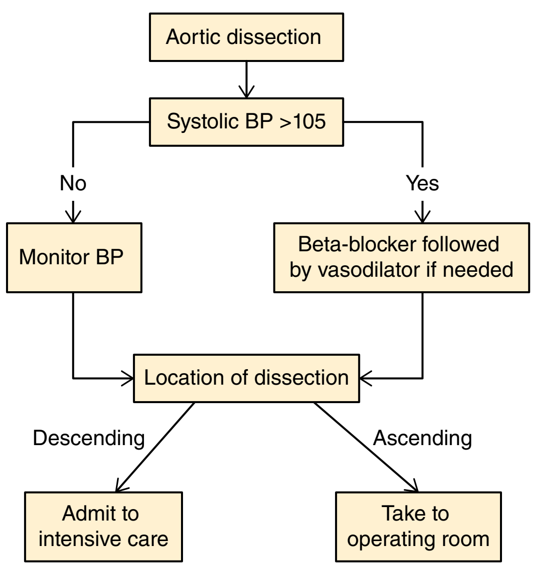
Treatment	Comments
Medical Pain control: • Morphine	
Beta-blockers (first line): • Labetolol (20 mg bolus followed by 0.5–2 mg/min) • Propranolol (1–10 mg bolus followed by 3 mg/h) • Esmolol (500 μg/kg bolus followed by 50 μg/kg/min)	Always ensure adequate beta-blockade prior to starting a vasodilator
Vasodilators (second line): • Nitroprusside (preferred second line agent; start at 0.2 μg/kg/min) • Nicardipine (start at 2.5 mg/h) • Enalaprilat (1.25 mg bolus)	Nitroprusside may cause cyanide toxicity and should be avoided in those with renal dysfunction or pregnancy Avoid hydralazine as it may increase shear stress and is less reversible than other methods of blood pressure control
Surgical Open repair	Ascending aortic dissection is generally managed with open repair
Endovascular repair	If a type B dissection requires surgical management, it often can be done with endovascular techniques

Prevention/management of complications

- If using nitroprusside, first ensure adequate beta-blockade as the vasodilation from nitroprusside may cause an increase in sympathetic tone and ultimately an increase in aortic shear stress.
- Avoid direct vasodilators such as hydralazine since they increase aortic wall shear stress.

Management/treatment algorithm (Algorithm 14.2)

Algorithm 14.2 Management of aortic dissection



CLINICAL PEARLS

- Rapid and sustained blood pressure reduction is the most important part of medical therapy.
- It is best to have an arterial line to safely facilitate this process.
- Aggressive pain management will increase patient comfort and also decrease blood pressure.

Special populations

Pregnancy

- Pregnancy and delivery are risk factors for aortic dissection.
- Management of the dissection remains the same; avoid nitroprusside because of possible fetal cyanide toxicity and use nicardipine instead.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- The 10-year survival rate of patients who leave the hospital is between 30% and 88%.
- Survival rates are similar for type A and type B dissections.
- Reoperation is required in up to 50% of patients after 10 years.

Reading list

Crawford ES. The diagnosis and management of aortic dissection. JAMA 1990;264:2537.
Debakey ME. Surgical management of dissecting aneurysms of the aorta. Thorac Cardiovasc Surg 1965;49:130.
Hagan PG. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA 2000;283(7):897.
Tsai TT. Acute aortic syndromes. Circulation 2005;112:3802.
Varon J. The diagnosis and management of hypertensive crisis. Chest 2000;118:214–27.

Guidelines

National society guidelines

Title	Source	Date and weblink
Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease	American Heart Association (AHA)	2010 http://professional.heart.org/idc/groups/ahaecc-internal/@wcm/@sop/documents/downloadable/ucm_423806.pdf

International society guidelines

Title	Source	Date and weblink
Guidelines on the Diagnosis and Treatment of Aortic Diseases	European Society of Cardiology (ESC)	2014 http://eurheartj.oxfordjournals.org/content/ehj/35/41/2873.full.pdf

Evidence

Type of evidence	Title and comment	Date and weblink
Meta-analysis	*Meta-analysis of usefulness of* D*-dimer to diagnose acute aortic dissection* D-dimer levels are useful in excluding dissection if the value is lower than 500 ng/mL.	2011 http://www.sciencedirect.com/science/article/pii/S0002914910027311

Images

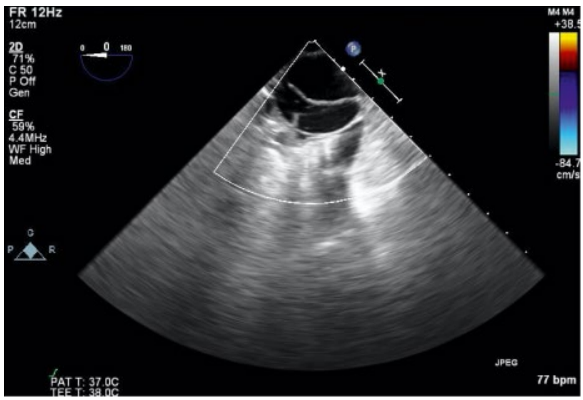


Figure 14.1 A TEE showing a true lumen and a false lumen with a dissection flap in the descending aorta.

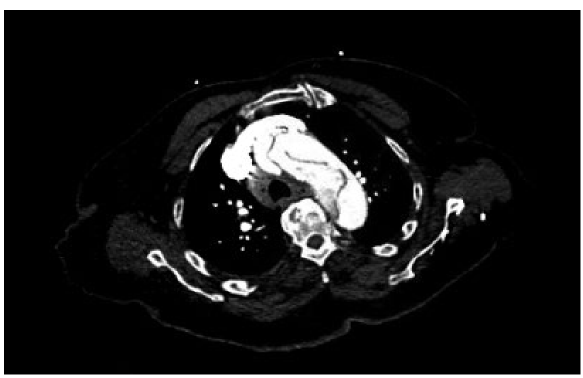


Figure 14.2 A CT angiogram showing an extensive aortic dissection in both the ascending and descending aorta.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 15

Cardiac Arrhythmias

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OVERALL BOTTOM LINE
- Heart rhythm disorders are a common occurrence in the ICU, and can either be the reason for admission or the consequence of a medical condition.
- The onset of arrhythmias can be a sign of systemic illnesses and management of the patient requires appropriate diagnostic tests and the correction of underlying abnormalities.
- Pharmacologic choices need to be tailored to the underlying clinical status of the patient.
- Urgent defibrillation/cardioversion is required for hemodynamically unstable atrial or ventricular arrhythmias.

Background

Disease classification

- Bradyarrhythmias (rate <60 bpm):
  - Sinus node dysfunction: sinus bradycardia/pauses/arrest.
  - AV block: first degree, second degree (Mobitz I/II), and complete.
- Tachyarrhythmias (rate >100 bpm):
  - Narrow complex (QRS <120 milliseconds): supraventricular origin.
  - Broad complex (QRS >120 milliseconds): either supraventricular with aberrant intraventricular conduction or ventricular origin (often the latter).

Incidence/prevalence

- The incidence of arrhythmia in the ICU patient is about 40%, with the most common underlying conditions being septic shock and respiratory failure.

Etiology

The '5T' and '5H' rule can be applied to diagnosing serious arrhythmias in the ICU setting:
- Thrombosis (pulmonary/cardiac), tamponade (cardiac), tension pneumothorax, toxins, trauma.
- Hypoxia, hypovolemia, hypothermia, hyper/hypokalemia, hydrogen ions (acidosis).

Pathology/pathogenesis

- Bradyarrhythmias:
  - Sinus node dysfunction: decreased automaticity due to age, drugs, etc.
  - AV block: either in the AV node or His–Purkinje system due to age, ischemia, drugs, infections.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- Tachyarrhythmias:
  - Increased automaticity: such as paroxysmal atrial tachycardia (AT) or multifocal atrial tachycardia (MAT).
  - Triggered activity: such as torsade des pointes or digoxin toxicity.
- Re-entry: most common cause of clinically significant tachycardias, e.g. atrioventricular nodal re-entrant tachycardia (AVNRT), atrioventricular re-entrant tachycardia (AVRT), atrial flutter (AFl), ventricular tachycardia (VT).

Predictive/risk factors

- Age >70 years old.
- Male gender.
- APACHE score >25.
- Underlying disease (cardiac/pulmonary/thyroid).
- Metabolic derangement.
- Volume fluctuations.
- Electrolyte disturbances.
- Vasopressors.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Risk of developing arrhythmias in the ICU can be minimized by addressing:
  - Inflammatory/infectious underlying processes, especially pulmonary.
  - Thyroid function.
  - Coronary perfusion.
  - Electrolytes and acid–base metabolism.
  - Intravascular depletion and anemia.
  - Use of inotropes, vasopressors, and sympathomimetic agonists.

Diagnosis

Although clinical history and laboratory tests are helpful, diagnosis is mainly based on ECG findings. Some common arrhythmias are defined below.

- *Sinus node dysfunction*: characterized by sinus bradycardia, sinus arrest, or pauses.
- *Second degree AV block, Mobitz I (Wenckebach)*: there is a progressive lengthening of the PR interval until a P wave is not conducted. There is only one non-conducted P wave. It is a result of delay within the AV node and is usually benign.
- *Second degree AV block, Mobitz II*: characterized by episodic and unpredictable failure of the His–Purkinje pathway to conduct the impulse from the atria to the ventricles. There is no change in the PR interval prior to or after the non-conducted P wave. Usually symptomatic and indicative of underlying disease of the His–Purkinje system, with high rates of progression to complete AV block.
- *Complete AV block*: this presents with AV dissociation – variable PR intervals – and an escape rhythm that is either junctional or ventricular and with a slower rate than atrial rhythm (Figure 15.1). This is produced due to a complete failure of the AV node to conduct any impulses from the atria to the ventricles.

- *Atrial fibrillation (AF)*: there are no distinct P waves (atrial activity can be usually seen, however it is not regular and occurs at rates >300 bpm). The RR intervals follow no repetitive pattern ('ventricular response irregularly irregular').
- *Supraventricular tachycardia (SVT)*: regular narrow complex rhythms at rates of 140–220 bpm. P (antegrade or retrograde) wave can be often seen, particularly in inferior leads and V1 (Figure 15.2).
- *Monomorphic ventricular tachycardia (VT)*: regular wide QRS tachycardia with QRS morphology inconsistent with aberrancy (Figure 15.3). Other features that can be seen include AV dissociation, capture beats (normal conduction system has momentarily conducted one sinus beat, in the midst of AV dissociation, to produce a QRS complex of normal duration), fusion beats (combination beats that result when sinus and ventricular complexes simultaneously activate the ventricular myocardium creating a hybrid complex), and positive or negative concordance throughout the precordial leads.
- *Polymorphic VT*: regular wide QRS tachycardia with frequent variations of the QRS axis, morphology, or both (Figure 15.4). *Torsade des pointes* ('twisting around points') is a subtype in which these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis. The peaks of the QRS complexes appear to 'twist' around the isoelectric line.

Differential diagnosis

Arrhythmia	Differential diagnosis	Features
Atrial fibrillation	Multifocal atrial tachycardia (MAT) Typical atrial flutter (AFl) with variable ventricular response	MAT: P waves can be seen (at least three different morphologies) AFl: underlying sawtooth waves
Narrow QRS tachycardias	AVNRT/AVRT AT/MAT Common AFl Atrial fibrillation (AF)	AVNRT/AVRT: breaks with adenosine AT/AFl: slow down with adenosine, but do not break. Sawtooth waves in AFl AF: irregular, no P waves
Wide QRS tachycardias	VT SVT with aberrance AF + WPW	VT: underlying heart disease. Dissociation P-QRS, captures/fusions. Precordial concordance SVT: breaks with adenosine. Baseline bundle branch block. Similar morphology/axis ECG baseline and tachycardia AF + WPW: irregular ventricular response, variation of QRS widening

Typical presentation

- The onset of all tachyarrhythmias is abrupt except sinus tachycardia, which is gradual. Symptoms can be palpitations, shortness of breath, dizziness, or chest pain – although underlying conditions may be driving these.
- Bradyarrhythmias: symptoms range from asymptomatic to dizziness or pre-syncopal or syncopal spells. There is shortness of breath from low cardiac output or worsening heart failure.

Clinical diagnosis

History

Diagnosis of arrhythmia is based mainly on the ECG. However, some features of the clinical history can be key:

- Pulmonary disease and cardiovascular risk factors are often associated with AF and atrial arrhythmias.
- AVNRTs/AVRTs are more typical in patients under 40 years old.

- A wide QRS tachycardia should be considered VT unless otherwise proven. VT should be suspected in patients with ventricular dysfunction, structural or valvular heart disease, myocardial scar due to a prior myocardial infarction, and in the post-infarct patient.
- Polymorphic VT associated with a normal QT interval is more typical in the setting of acute myocardial ischemia. When associated with an acquired prolonged QT, drugs or magnesium depletion (as in cases of torsade des pointes) are underlying causes.

Physical examination

- In the ICU setting, this should focus on signs of hemodynamic compromise, which may require urgent cardioversion.
- In wide QRS tachycardia, signs of underlying cardiomyopathy (cardiomegaly, diastolic or significant systolic murmur, abnormal findings in the ECG such as bundle branch block or abnormal repolarization) make the diagnosis of VT highly probable.
- In wide QRS tachycardia, a pounding sensation in the neck is more often related to AVNRT. This finding is produced due to simultaneous contraction of the atrium and ventricle – when the AV valve is closed – that propels venous flow backwards.

Useful clinical decision rules and calculators

The ECG criteria for VT diagnosis are:

- Absence of typical right or left bundle branch block (RBBB/LBBB) morphology.
- Extreme axis deviation ('northwest axis'): QRS is positive in aVR and negative in I and aVF.
- Very broad complexes: ≥160 milliseconds in LBBB morphology and ≥140 milliseconds in RBBB morphology.
- AV dissociation: variable PR interval with P and QRS complexes at different rates; this is highly specific.
- Capture/fusion beats.
- Positive or negative concordance throughout the precordial leads.
- Brugada's sign: the distance from the onset of the QRS complex to the nadir of the S wave is >100 milliseconds.
- Josephson's sign: notching near the nadir of the S wave.
- RSR complexes with a taller 'left rabbit ear': this is the most specific finding in favor of VT. This is in contrast to RBBB, where the right rabbit ear is taller.

Laboratory diagnosis

List of diagnostic tests

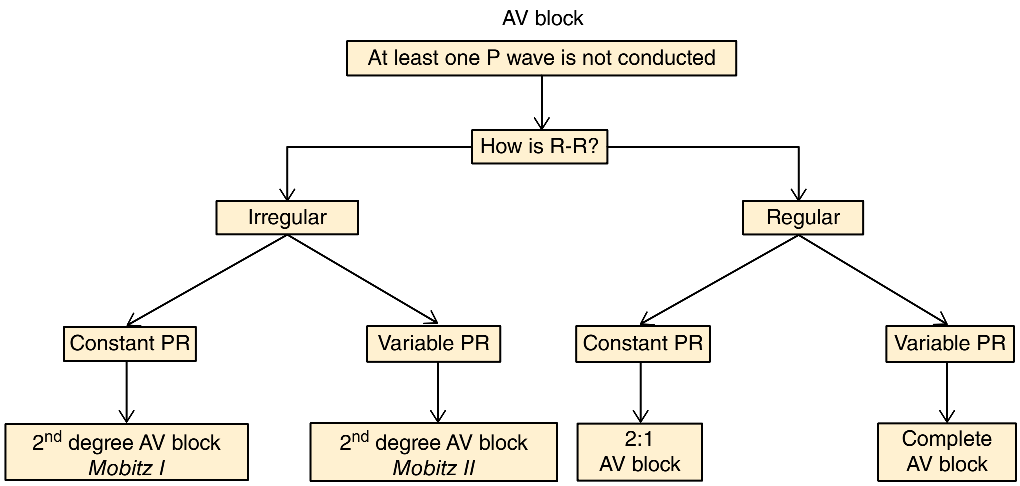
- Potassium has a pronounced effect on both conduction and automaticity, with even small variations of its concentration. Consequently, of all the electrolytes, disturbed potassium metabolism accounts for the vast majority of clinical arrhythmias (e.g complete AV block, VF).
- Calcium, magnesium, and sodium affect the action potential and induce experimental arrhythmias (MAT or torsade des pointes, in case of magnesium) but at concentrations which are unphysiologic.
- Concentration of digoxin should be monitored, especially in patients with depressed renal function.

Imaging modalities

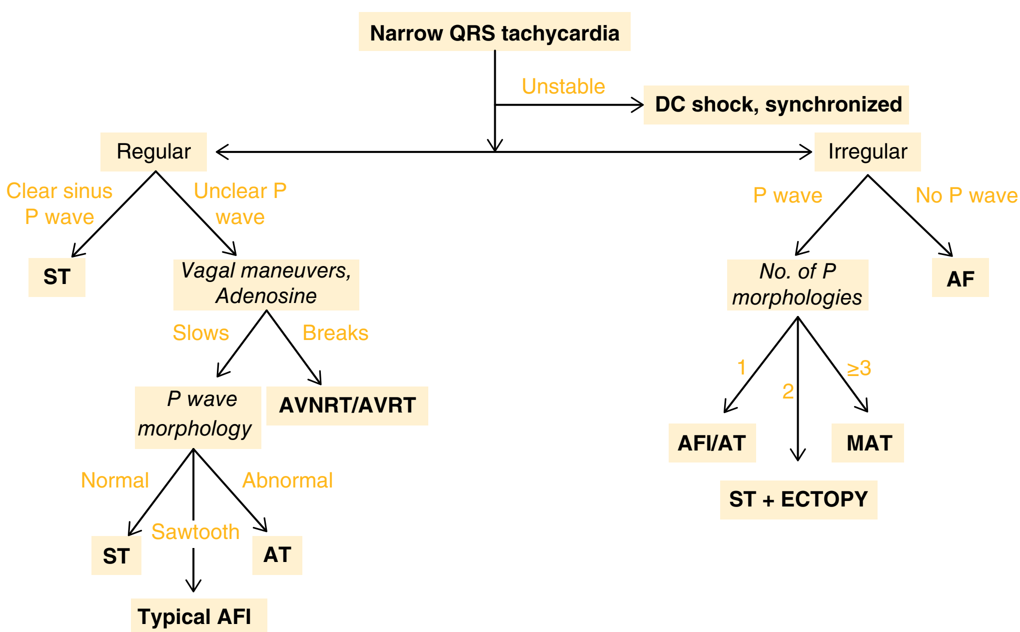
- Transthoracic echocardiogram should be performed in patients with unexplained ventricular arrhythmias in order to rule out structural heart disease. Urgent echocardiogram should be performed in case of sudden hemodynamic worsening or uncontrolled arrhythmias.

Diagnostic algorithms (Algorithms 15.1–15.3)

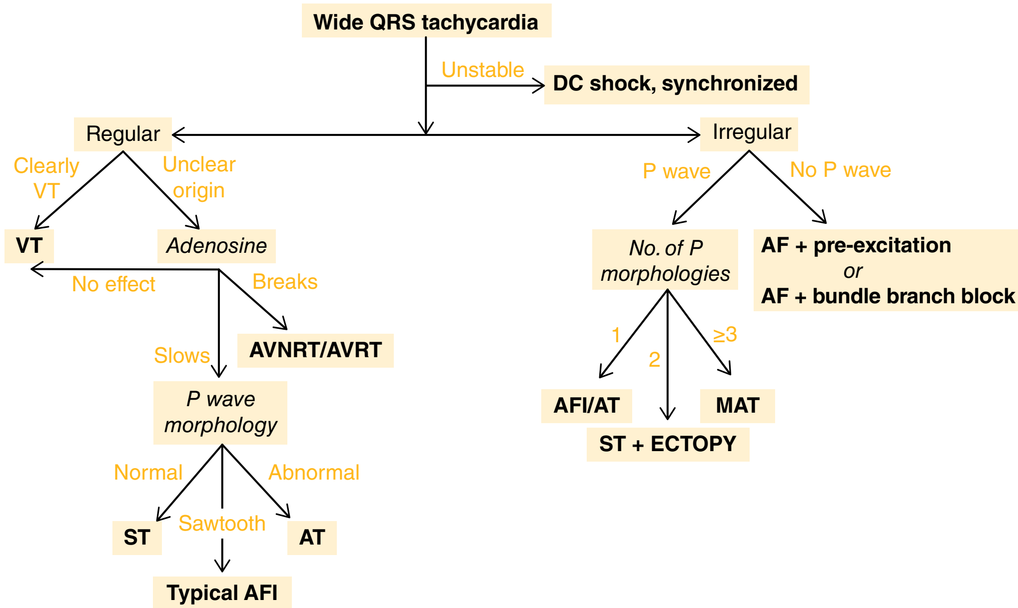
Algorithm 15.1 Diagnostic algorithm for AV block (Adapted from Neumar et al. 2010)



Algorithm 15.2 Diagnostic algorithm for narrow QRS tachycardia (Adapted from Tracy & Boushahri 2014)



Algorithm 15.3 **Diagnostic algorithm for wide QRS tachycardia (Adapted from Tracy & Boushahri 2014)**



Potential pitfalls/common errors made regarding diagnosis of disease

- A wide complex tachycardia of ventricular origin can be misdiagnosed as SVT with aberrant conduction. Administration of verapamil in cases of diagnostic uncertainty may result in profound hemodynamic deterioration.
- Atrial flutter with a variable degree of AV block and MAT are often misdiagnosed as AF. This usually happens because the ECG shows irregular ventricular response and this is automatically taken as AF.

Treatment

Treatment rationale

Bradyarrhythmias

Treat any reversible causes. When causing significant hemodynamic compromise:

- Acute treatment with one of the following:
  - *Atropine*: 0.5 mg IV, repeated if necessary every 3–5 minutes to a total dose of 3 mg. This is more effective in sinus node dysfunction or in block at the level of the AV node. It is unlikely to be effective when block is at or below the bundle of His, or in transplanted hearts (lack vagal innervation).
  - *Isoprenaline*: 10–20 μg IV, repeated according to clinical response, followed by an infusion at 1–4 μg/min.
- Do not delay treatment with transcutaneous pacing or a chronotropic agent in order to give atropine/isoprenaline. If these agents are ineffective, consider temporary pacing.
- If pacing is delayed or not available, start infusion of one of the following:
  - *Dopamine*: 2–10 μg/kg/min, titrated according to clinical response.
  - *Epinephrine*: 2–10 μg/min, titrated according to clinical response.
- In the presence of bradycardia and hemodynamic compromise, look for myocardial infarction or poor ventricular function.

Tachyarrhythmias

- Severe hemodynamic compromise induced by any tachyarrhythmia should be treated with emergent electric DC cardioversion.
- Sedation is indicated when tolerated.
- Synchronize shocks with the QRS complex except in cases of cardiac arrest due to VF. Biphasic waveform (100–200 J energy) is preferable than monophasic (200–400 J). Pads placed anterior to posterior provide greater efficacy.

Atrial fibrillation

Reversion to sinus rhythm

- Electric DC cardioversion: as previously indicated.
- Pharmacologic cardioversion: within 48 hours after onset in clinically and hemodynamically stable patients.
  - *Ibutilide*: more effective but not specifically tested in ICU population:
    - Patient <60 kg: 0.01 mg/kg IV over 10 minutes.
    - Patient >60 kg: 1 mg IV over 10 minutes.

May repeat once if arrhythmia does not terminate.

- *Amiodarone*: offers a safer profile: 150 mg IV over 10 minutes, then IV drip 1 mg/min for 6 hours followed by 0.5 mg/min for 19 hours (total 1 g over 24 hours).

Heart rate control

If onset >48 hours ago or in stable patients in whom conversion to sinus rhythm is hardly expected while underlying process is still active (postoperative, sepsis, etc.).

- Beta-blockers as first line:
  - *Metoprolol*: 2.5–5.0 mg IV bolus over 2 minutes, up to three doses.
  - *Esmolol*: 500 μg/kg IV bolus over 1 minute, then 50–300 μg/kg/min IV.
- Calcium-channel blockers are a good alternative, but must be avoided if pre-excited AF, heart failure, and reduced ejection fraction:
  - *Verapamil*: 0.075–0.15 mg/kg IV bolus over 2 minutes, may give an additional 10.0 mg after 30 minutes if no response, then 0.005 mg/kg/min infusion.
  - *Diltiazem*: 0.25 mg/kg IV bolus over 2 minutes, then 5–15 mg/h.
- Amidarone, a suitable alternative when previous drugs are not tolerated: 300 mg IV over 1 hour, then 10–50 mg/h over 24 hours.
- Digoxin: onset of action >1 hour. Use with caution if there is decreased renal function. Use one of the following doses:
  - 0.25 mg IV every 2 hours (up to 1.5 mg in 24 hours).
  - 0.5 mg IV bolus + 0.25 mg IV every 3–4 hours (up to 1.5 mg in 24 hours).

AVNRT/AVRT

- Perform vagal-enhancing maneuvers as first step.
- If ineffective, use adenosine: 6 mg IV over 1–3 seconds (may be given IO) followed by rapid flush with 20 mL of saline. If no conversion within 1–2 minutes give 12 mg IV, repeat a second time if necessary (30 mg total; dose should be reduced by 50% when injected through a central venous catheter).
- Verapamil and diltiazem (dose regimen as previously described) are also very effective, but adenosine is faster and produces less depression of cardiac function. Use verapamil/diltiazem with caution in

case of pre-excitation as they may accelerate ventricular rate. In patients hemodynamically compromised, amiodarone may be an option.

Atrial tachycardia/MAT

Discontinuation/correction of predisposing factors can be effective itself (mainly electrolyte disturbances in MAT). In case it is not, drugs for heart rate control such as metoprolol or verapamil have been demonstrated to be effective (dose regimen as previously described).

Monomorphic VT

- *Amiodarone* as first line: 150 mg IV over 10 minutes, may repeat every 10 minutes as needed; then IV drip 1 mg/min for 6 hours followed by 0.5 mg/min for 18 hours (maximum cumulative dose 2.2 g over 24 hours).
- *Lidocaine*: more effective in the setting of an acute coronary event: 1–1.5 mg/kg IV, may repeat 0.5–0.75 mg/kg every 5–10 minutes (maximum cumulative dose 3 mg/kg); then IV drip 1–4 mg/min.
- *Procainamide* (but not indicated if QT is prolonged): 15–18 mg/kg over 25–30 minutes or 100 mg given no faster than 50 mg/min, may repeat every 5 minutes (maximum cumulative dose 1 g); then IV drip 1–4 mg/min.
- *Sotalol* (but watch for proarrhythmic effect): 1–1.5 mg/kg (or 100 mg) at a rate of 10–20 mg/min.

Polymorphic VT

- Intravenous magnesium can be useful as first step:
  - *Magnesium*: 2 g IV over 5–30 minutes, and repeat this dose 10 minutes later if needed. Follow with a continuous infusion of 1 g/h for the next 6 hours.
- When QT interval is normal, look for myocardial ischemia.
- When QT interval is prolonged (torsade des pointes), correct precipitant factors such as electrolytes or drugs. Ventricular pacing or isoproterenol can be also effective, as QT interval shortens as heart rate rises.

Recurrent VT/VF–electrical storm

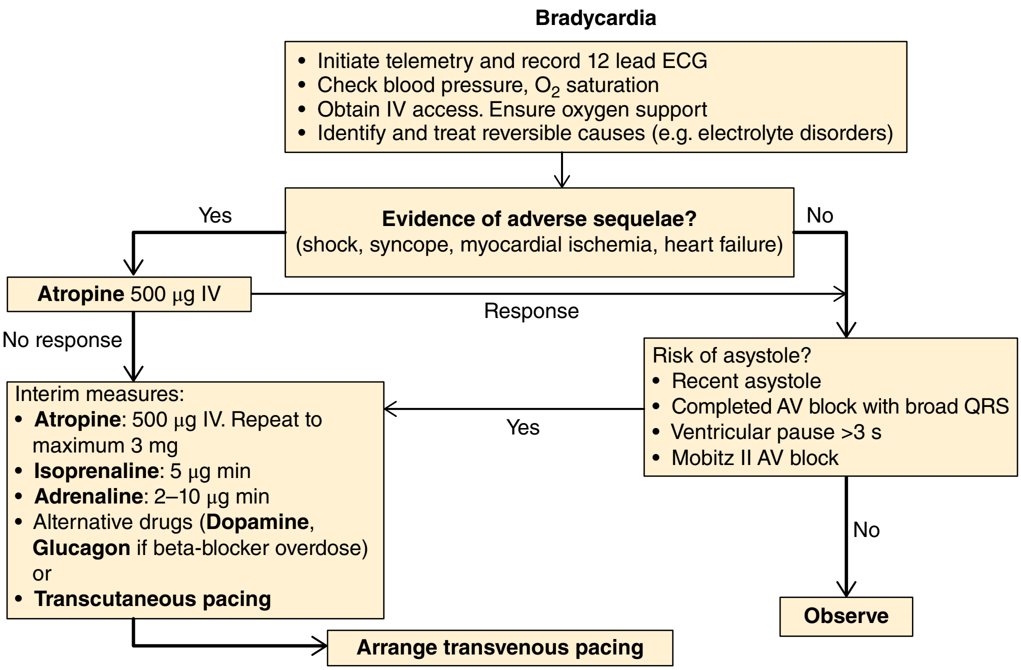
Correct the underlying and reversible causes as first step. The most useful drugs in an electrical storm are amiodarone and beta-blockers. Ventricular pacing or isoproterenol can be useful in cases of channelopathy. In case of VF, DC shock (not synchronized, maximum energy) is the treatment.

Prevention/management of complications

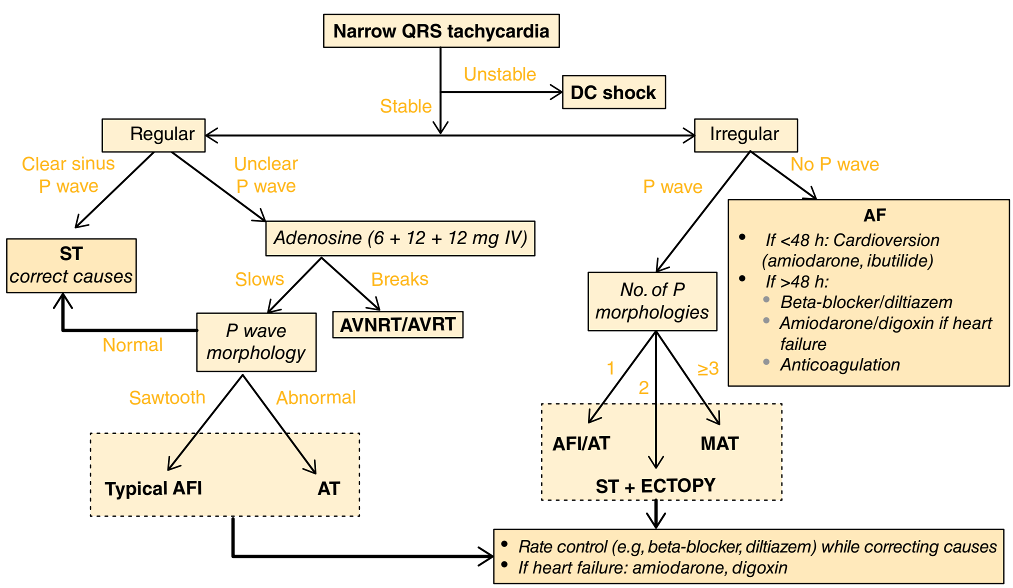
- Do not attempt DC cardioversion in the setting of uncorrected hypokalemia or digoxin toxicity (risk of developing resistant VF).
- Procainamide, ibutilide: prolong QT interval. Stop infusion if QT increases >50%
- Calcium-channel blockers: cardiac depression and hypotension. Vasopressors may be required.
- Digoxin toxicity (complete AV block, joint tachycardia): in general, effects disappear completely in 2–3 days after digoxin is stopped. In the meantime, transvenous temporary pacing may be required. In extreme cases in which immediate neutralization of digoxin effect is needed, antidigoxin antibodies may be useful.
- Adenosine: contraindicated in patients with asthma due to bronchospasm induction. Bronchodilators may be required.
- Calcium-channel blockers, digoxin, and adenosine: may accelerate ventricular rate in pre-excitation as they shorten the refractory anterograde period of the pathway. Emergent defibrillation or DC cardioversion may be required.

Management/treatment algorithms (Algorithms 15.4–15.6)

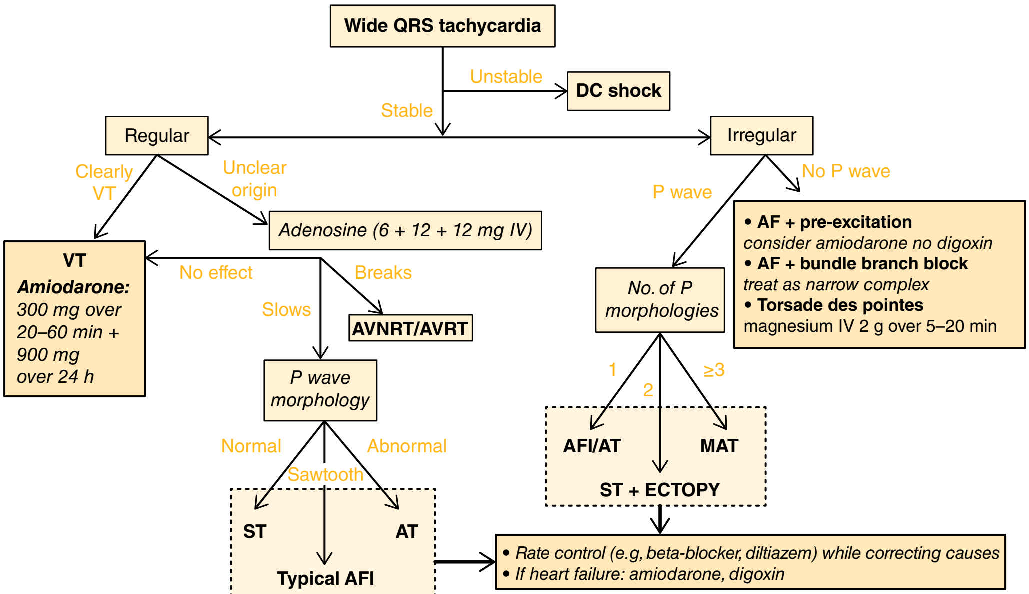
Algorithm 15.4 Treatment algorithm for AV block (Adapted from Neumar et al. 2010)



Algorithm 15.5 Treatment algorithm for narrow QRS tachycardia (Adapted from Tracy & Boushahri 2014)



Algorithm 15.6 Treatment algorithm for wide QRS tachycardia (Adapted from Tracy & Boushahri 2014)



CLINICAL PEARLS

- In complete AV block, escape rhythm with wide QRS, and ventricular rate <40 bpm usually means an infra-His escape, distal from the AV node (the more wide the QRS, the more distal the escape, unless bundle branch block pre-exists). In this setting, atropine or isoprenaline should be used carefully as they may increase even more the degree of block and worsen the escape heart rate.
- Digoxin and calcium channel blockers should be avoided (or, at least, used carefully) if accessory pathway is suspected. Both drugs can accelerate ventricular rate further by shortening the anterograde refractory period of the pathway.
- Wide QRS tachycardia should be always considered initially as VT unless other origin is proven.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Uncontrolled atrial tachyarrhythmias tend to produce left ventricular dysfunction and subsequent heart failure symptoms due to related tachycardiomyopathy, unless the heart rate is controlled.
- Narrow QRS tachycardias are rarely a lethal condition themselves. However, their adverse consequences may worsen significantly the fragile status of an ICU patient.
- It is highly probable that Mobitz II AV block will need ventricular pacing, as it tends to evolve to complete AV block.
- Ventricular tachycardia is an important cause of sudden death. It is important to distinguish high risk groups (cardiomyopathy, left ventricular dysfunction, coronary artery disease) who would benefit from an implantable cardioverter defibrillator (ICD) from patients with idiopathic VT without structural heart disease, who have a more benign prognosis.

Reading list

Marino PL. Marino's The ICU Book, 4th edition. Philadelphia: Wolters Kluwer, 2013.

Neumar RW, et al. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010;122(18 Suppl 3):S729–67.

Tracy C, Boushahri A. Managing arrhythmias in the intensive care unit. Care Clin 2014;30:365–90.

Tubaro M, Vranckx P, Price S, Vrints C (eds). The ESC Textbook of Acute and Intensive Cardiac Care, 2nd edition. Oxford: Oxford University Press, 2015.

Suggested websites

www.criticalcare.theclinics.com

www.esicm.org/icm-search

www.heart.org

Guidelines

National society guidelines

Title	Source	Date and reference
Guideline for the Management of Adult Patients with Supraventricular Tachycardia	American College of Cardiology (ACC)/ American Heart Association (AHA)/Heart Rhythm Society (HRS)	2016 J Am Coll Cardiol 2016;67(13):e27–115
Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care	AHA	2015 Circulation 2015;132:S315–67
Guideline for the Management of Patients with Atrial Fibrillation	AHA/ACC/HRS	2014 J Am Coll Cardiol 2014;64(21);e1–76
Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary: a Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines	American College of Cardiology Foundation (ACCF)/AHA	2013 Circulation 2013;127:529–55
Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care	AHA	2010 Circulation 2010;122(18 Suppl 3):S729–67
Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines	ACC/AHA/HRS	2008 Circulation 2008; 117(21):e350–408

International society guidelines

Title	Source	Date and reference
Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death	European Society of Cardiology (ESC)	2015 Eur Heart J 2015;36:2793–867
Guidelines for the Management of Atrial Fibrillation. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)	ESC	2010 Eur Heart J 2010;31:2369–429
Guidelines for Cardiac Pacing and Cardiac Resynchronization Therapy: The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association	ESC	2007 Eur Heart J 2007;28(18):2256–95

Evidence

Type of evidence	Title and comment	Date and reference
Prospective trial	*Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators* A prospective, multicenter trial that shows that amiodarone in low doses is more effective than sotalol or propafenone, with no significant increasing of risk of complications	2000 N Engl J Med 2000;342(13):913–20
Retrospective analysis	*Relationship of paroxysmal atrial tachyarrhythmias to volume overload: assessment by implanted transpulmonary impedance monitoring* Retrospective analysis that showed that worsening pulmonary congestion is associated with increased frequency of atrial tachyarrhythmias (AT) in patients with left ventricular dysfunction.	2009 Circulation 2009;2:488–94
Review	*Diagnostic criteria of broad QRS complex tachycardia: decades of evolution* Despite all available criteria, broad complex tachycardias are still misdiagnosed or remain undiagnosed.	2011 Europace 2011;13:465–72

Images

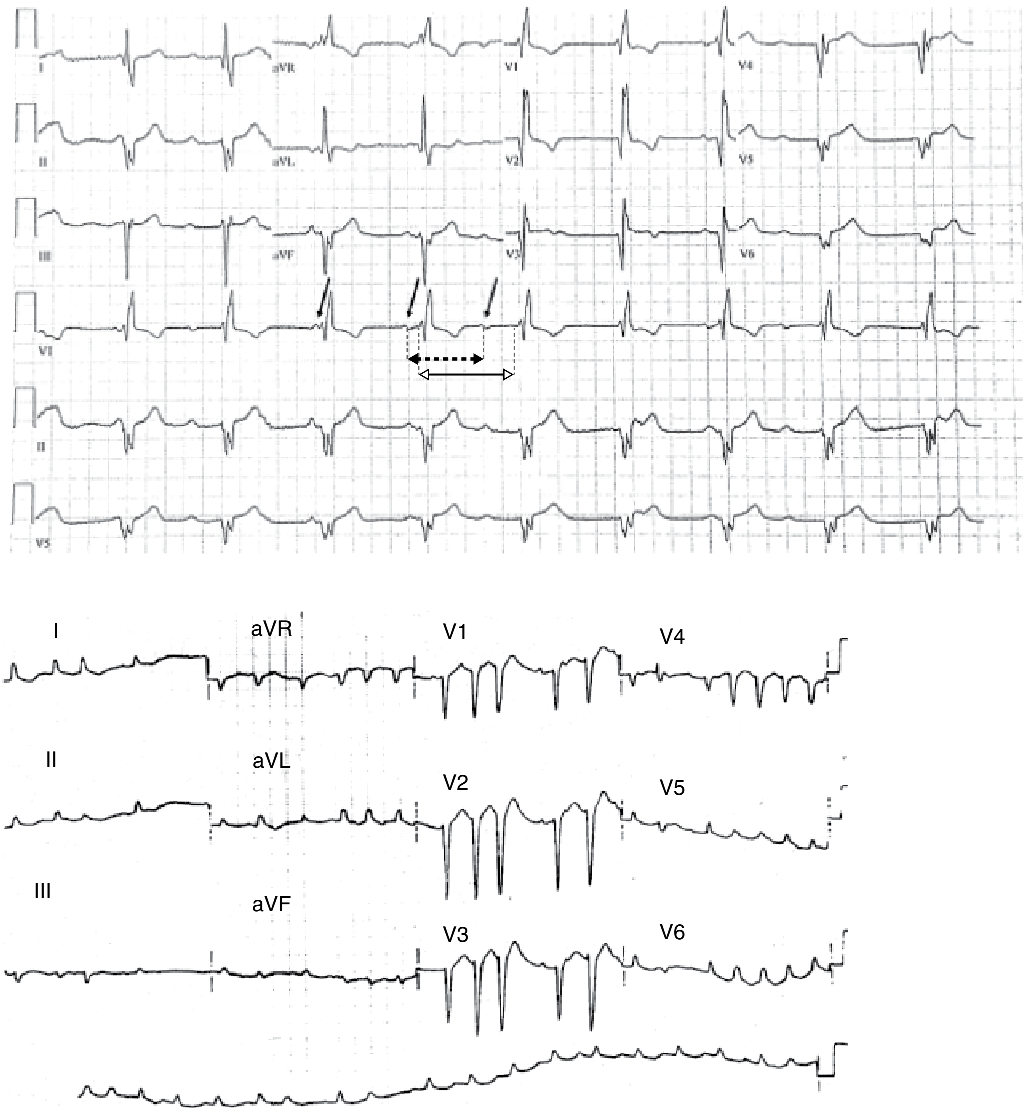
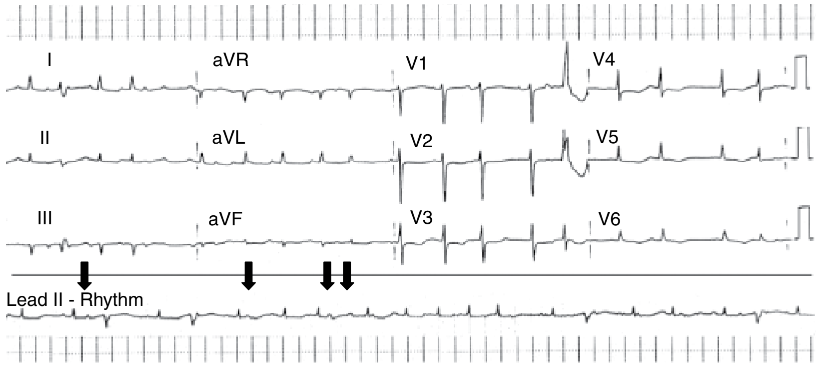
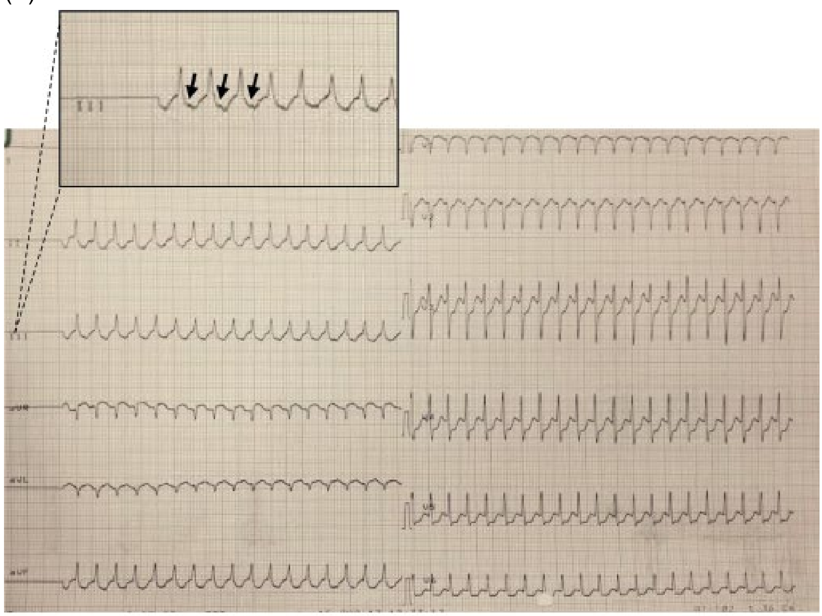


Figure 15.1 ECG 1: complete AV block in patient with baseline bifascicular block. Atrial activity (black arrows) at a rate of 70 bpm (bold dashed arrow), completely dissociated of ventricular escape rhythm. The latter has a QRS of 120 ms but its morphology is similar to baseline ECG and has a rate >45 bpm (open arrow). Thus, this is most likely a junctional escape. (Source: personal collection.)



(A)



(B)

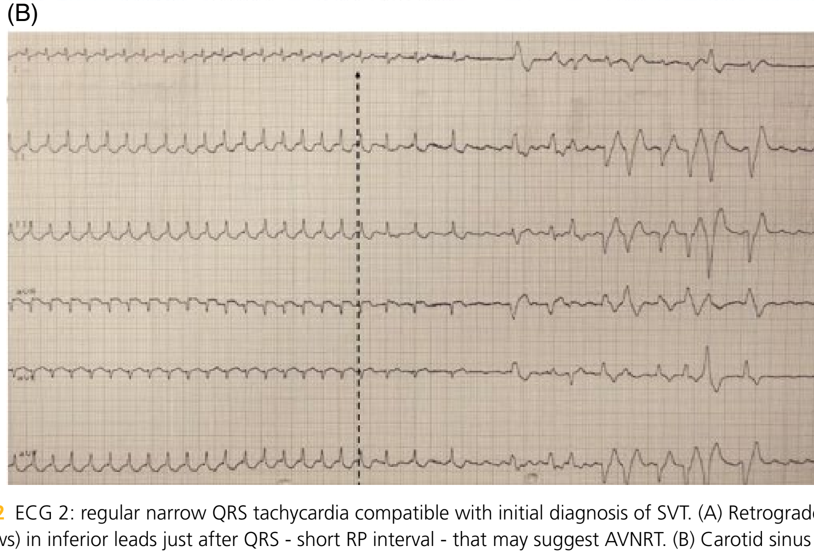


Figure 15.2 ECG 2: regular narrow QRS tachycardia compatible with initial diagnosis of SVT. (A) Retrograde P waves (black arrows) in inferior leads just after QRS - short RP interval - that may suggest AVNRT. (B) Carotid sinus pressure (starts from the black arrow) initially slows down ventricular rate and finally breaks tachycardia. This demonstrates that AV node is a critical point within the circuit of tachycardia. (Source: personal collection.)

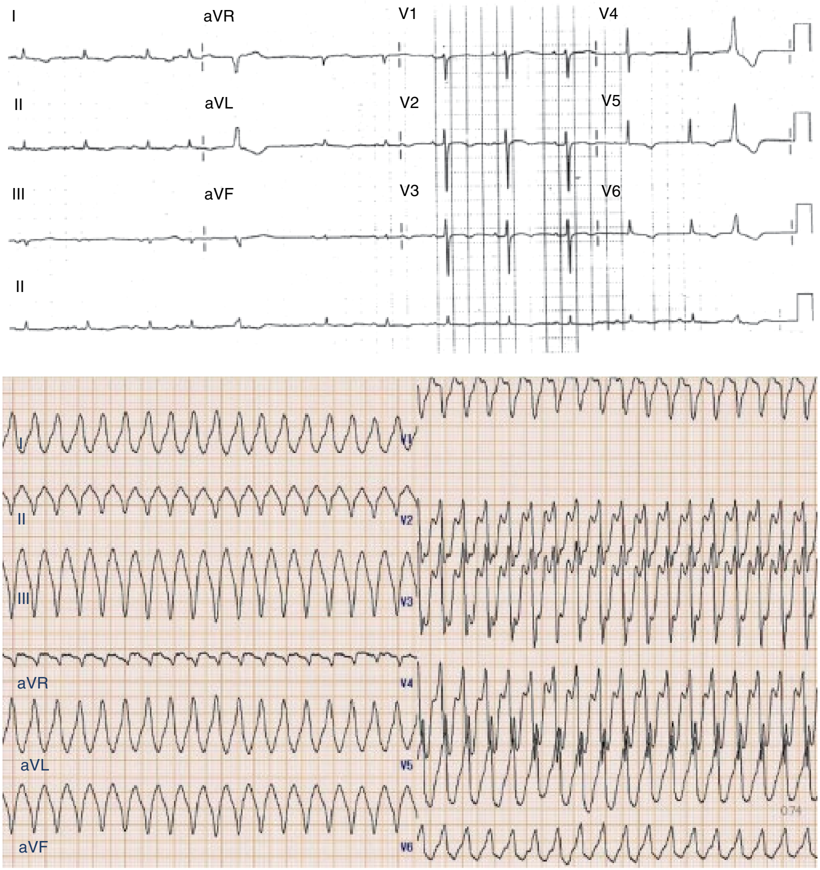


Figure 15.3 ECG 3: VT. Very wide regular QRS tachycardia with atypical bundle branch block pattern. (Source: personal collection.)

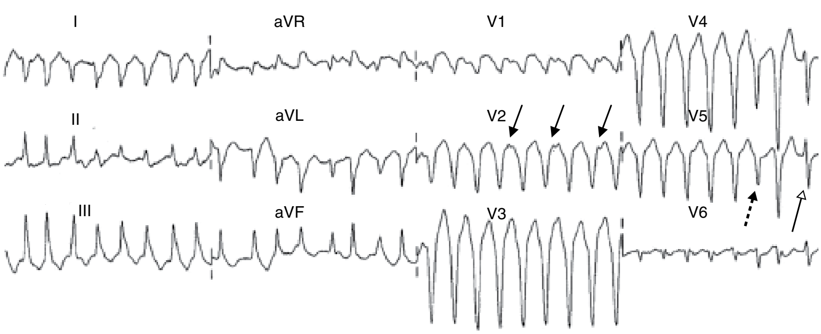


Figure 15.4 ECG 4: wide complex tachycardia, presented as atypical left bundle branch block pattern, negative concordance throughout the precordial leads, AV dissociation (black arrow), capture (bold dashed arrow), and fusion beats (open arrow). These features are compatible with diagnosis of VT. However, capture and fusion beats give the incorrect impression of irregularity, which may lead to misdiagnosis as pre-excited/aberrated AF. (Source: personal collection.)

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions and case study.

with website

CHAPTER 16

Acute Coronary Syndromes

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OVERALL BOTTOM LINE

- Acute coronary syndromes (ACS) are potentially life-threatening conditions that require emergent medical attention to reduce the risk of morbidity and mortality.
- Medical therapy with anticoagulation and dual antiplatelet agents is proven to be effective in the treatment of ACS.
- ST elevation myocardial infarction (STEMI) is a medical emergency that requires emergent revascularization in addition to medical therapy.
- Patients with non-ST elevation ACS (unstable angina and non-ST elevation myocardial infarction) should be risk stratified. Those who are low risk can be managed medically while those who are high risk should proceed with early revascularization.
- Behavior modification such as smoking cessation, diet, and exercise are proven to be effective in both the primary and secondary prevention of coronary artery disease.

Background

Definition of disease

Acute coronary syndromes are defined by the presence of symptoms consistent with myocardial ischemia including chest pain and shortness of breath. Types of acute coronary syndrome are further specified by the presence or absence of ECG changes, and/or myocardial biomarkers.

Disease classification

Acute coronary syndromes can be viewed as three different clinical syndromes:

- ST elevation myocardial infarction (STEMI).
- Non-ST elevation myocardial infarction (NSTEMI).
- Unstable angina (UA).

Incidence/prevalence

- Incidence of STEMI: 50 cases per 100 000 patients.
- Incidence of NSTEMI: 158 cases per 100 000 patients.

Etiology

- Exposure to multiple risk factors as described later result in inflammation within the coronary arteries and formation of lipid-laden plaques.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- Plaques with a thin fibrous cap and large lipid core are prone to rupture, resulting in exposure of prothrombotic factors within the atheroma to blood and subsequent thrombus formation.
- Thrombus results in total or partial occlusion of the coronary artery lumen causing ischemia and, if severe enough, infarction.

Pathology/pathogenesis

- The pathogenesis of ACS is as simple as a mismatch between myocardial demand and its blood supply causing ischemia and, when severe enough, infarction. For the purpose of this chapter we focus on the formation of the atheromatous plaque, and its rupture, resulting in coronary thrombosis.
- Plaque starts as a fatty streak within the intima of blood vessels. At first, circulating LDL molecules aggregate within the intima of the coronary arteries. The oxidation of these LDL molecules results in an inflammatory reaction within the intima. Endothelium is stimulated resulting in the expression of cellular adhesion molecules. Chemoattractants and cytokines are released in the setting of this inflammation, causing circulating monocytes to migrate into the intima and differentiate into macrophages. Macrophages then scavenge oxidized LDLs and transform into foam cells, and subsequently undergo apoptosis. The apoptosis of foam cells results in the formation of a necrotic lipid rich core in some plaques (Figure 16.1).
- Several characteristics make a plaque more likely to rupture, including a larger necrotic lipid core, presence of inflammatory cells, and a thin fibrous cap.
- Often the culprit lesions of ACS are not flow limiting prior to rupture. These lesions tend not to be heavily calcified, in contrast to the high grade stenotic lesions that are more associated with chronic ischemic coronary disease.
- Thrombosis occurs when there is a disruption in the overlying protective endothelium and exposure of blood to the thrombogenic plaque core. This can occur via plaque rupture due to a weak and thinning fibrous cap or from erosion.
- If the thrombus is nearly or completely occlusive, the result is mural infarction and thus a STEMI. In the case of a dynamic or incompletely occlusive thrombus, non-ST elevation acute coronary syndromes (NSTE-ACS) such as NSTEMI or UA occur (Figure 16.2).

Predictive/risk factors

Risk factor	Odds ratio
Current smoking	2.9
Diabetes	2.4
Hypertension	1.9
Obesity (3rd vs. 1st tertile)	1.6
Psychosocial stress	2.7
Apo B/Apo A1 ratio (5th vs. 1st quintile)	3.3

Prevention

Both primary and secondary prevention in cardiovascular disease is largely a matter of managing the known risk factors stated earlier. Some of the strongest interventions for prevention of cardiovascular disease include smoking cessation, blood pressure control, cholesterol-lowering medications, weight loss, and good management of diabetes.

Screening

To date there are no tests that are regularly used to screen for cardiovascular disease in asymptomatic patients.

- A pooled cohort atherosclerotic cardiovascular disease (ASCVD) risk calculator can be used for patients between 40 and 79 years of age to determine the 10 year risk of cardiovascular disease and stroke. However, this has never been validated in the literature as a screening tool.
- Other potential screening tests for cardiovascular disease include high sensitivity C-reactive protein, coronary calcium score, and ankle-brachial index. These tests likewise have not been validated by clinical trials as screening tests. They currently hold a class IIB recommendation in the ACC guidelines for assessment of cardiovascular risk as adjunct tests. They may be considered for additional risk stratification if there is still a level of uncertainty regarding starting pharmacologic therapy after using the ASCVD risk calculator.

Primary prevention

- Smoking cessation is one of the most effective interventions in primary prevention of cardiovascular disease.
- Hypertension is well known to be a significant risk factor for cardiovascular disease and stroke. Recent guidelines recommend keeping blood pressure at <140/90 mmHg in patients aged 30–59 and <150/90 mmHg in patients over 60 years. However, new data from the SPRINT trial suggest that a lower blood pressure goal of <130/80 mmHg in patients with high cardiovascular risk may reduce the risk of major cardiac events even further.
- LDL-lowering therapy with statins has been demonstrated to be effective primary prevention in patients at high risk for cardiovascular disease. Newer data suggest that statins also have a significant impact on primary prevention in patients with lower risk for cardiovascular disease.
- Aggressive weight loss interventions have been shown to improve blood pressure and insulin resistance. However to date they have not shown to have a significant effect on cardiovascular events.
- Although low dose aspirin has clearly demonstrated a benefit in secondary prevention of cardiovascular disease the picture is less clear in primary prevention. Current USPSTF guidelines recommend low dose aspirin for primary prevention in adults 50–69 years of age with a >10% 10 year ASCVD risk.

Secondary prevention

Similar to primary prevention, much of the evidence in secondary prevention of cardiovascular disease is in managing the main risk factors:

- Smoking cessation plays a large role in secondary prevention of cardiovascular disease, and currently holds a class I recommendation in the guidelines.
- Blood pressure with a goal of 140/90 mmHg holds a class I recommendation in current guidelines for secondary prevention as well. However, as described, the data from the SPRINT trial may provide evidence for a lower blood pressure goal in the future.
- High intensity statin therapy has a class I recommendation for secondary prevention in patients with ACS and no contraindication to statins.
- Lifelong antiplatelet therapy with aspirin as well as dual antiplatelet therapy with a P2Y12 inhibitor for up to 12 months has a class I recommendation for secondary prevention in patients with ACS.
- Beta blockers are effective in secondary prevention for patients with ACS.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Patients with ACS typically present with persistent chest pain that is most commonly retro-sternal and can radiate to either or both arms, the jaw, and neck. Other aspects of the history that should increase suspicion for ACS include older age, family history of coronary disease, if the patient is male, has a personal history of coronary disease, or has other risk factors for ACS such as diabetes and hyperlipidemia.
- Elderly patients and women are more likely than others to present with atypical symptoms such as epigastric pain, indigestion, and stabbing pleuritic chest pain.
- Physical examination is not sensitive or specific in ACS and can be completely normal. Some findings that can occur include an S4 gallop, a systolic murmur in the setting of acute mitral insufficiency, or a paradoxical splitting of S2 in the setting of a new bundle branch block.
- Obtaining serial ECGs can help make the diagnosis of ACS and is critical in initial clinical decision making.
- Cardiac troponin helps to confirm the diagnosis of myocardial infarction, while CXR or CT scan helps to assess for other causes of chest pain such as pneumothorax and aortic dissection.

Differential diagnosis

Differential diagnosis	Features
Aortic dissection	Patient may complain of chest pain radiating to the back. On physical examination the patient may have different blood pressures in different arms. Diastolic murmur can be present in dissection if it resulted in aortic insufficiency. CXR may demonstrate mediastinal widening
Pericarditis	Patient may have a history of a recent viral illness. Pain is typically positional, made worse by lying flat and better by leaning forward. Pericardial friction rub may be appreciated on examination, or muffled heart sounds. ECG typically demonstrates diffuse ST elevation with PR depressions. Echocardiogram may demonstrate pericardial effusion
Pulmonary embolism	Patients typically present with shortness of breath and pleuritic chest pain. They may give a history of recent prolonged immobilization such as recent surgery. They may also have a history of malignancy or family history of blood clots. ECGs most commonly show sinus tachycardia, however they may demonstrate evidence of right ventricular strain such as new right bundle branch block, or rightward axis
Pneumothorax	Patient may give a history of recent chest wall trauma. Patient will likely present with shortness of breath and pleuritic-type chest pain. Physical examination may demonstrate decreased breath sounds and tracheal deviation. CXR or CT or bedside ultrasound all can establish the diagnosis
Diffuse esophageal spasm	Differentiating features of presentation include dysphagia of solids and liquids. Diagnostic modalities that help to make the diagnosis include endoscopy, barium swallow, and esophageal manometry

Typical presentation

- ACS most commonly present with what are referred to as ‘typical’ symptoms. Typical symptoms are described as a pressure or aching in the substernal or left chest areas, classically radiating to one or both arms. The pain can also radiate to the jaw, back, and shoulders. Chest pain in ACS tends to be more

diffuse and not well localized, commonly presenting with a crescendo pattern, typically taking several minutes before reaching its highest intensity.

- Pain lasting from 10 to 30 minutes is more likely to represent UA, whereas pain lasting more than 30 minutes is more indicative of myocardial infarction or non-cardiac pain.

Clinical diagnosis

History

- When approaching a patient with chest pain there are several aspects of the history to consider. Typical symptoms of ACS occur in the substernal or left chest area, and often radiate to one or both arms as well as the jaw and back. The duration can help distinguish between cardiac and non-cardiac pain, as pain that lasts for a few seconds or conversely for several days continuously is less likely to represent cardiac chest pain.
- Alleviation of pain with rest or nitroglycerine is classically thought to be more indicative of cardiac pain. However, several studies have shown that such factors are limited in their ability to distinguish cardiac from non-cardiac pain.
- Other symptoms associated with ACS can include nausea, vomiting, diaphoresis, and shortness of breath. It is important to consider that as many as one-third of patients with acute myocardial infarction can present without chest pain. In particular women, older patients, and diabetics are more likely to present without typical symptoms. For this reason, it is critical to assess risk factors for coronary artery disease when taking a history, as this will help to raise or lower your suspicion for ACS.

Physical examination

- Physical examination is often unrevealing in patients presenting with ACS.
- In the setting of acute myocardial ischemia patients may develop heart failure. Physical exam findings such as rales on respiratory auscultation and elevated jugular venous pulsation may be appreciated in these patients. Other physical exam findings that can occur with ACS include a holosystolic murmur secondary to mitral regurgitation in the setting of papillary muscle dysfunction, S4 gallop, or paradoxical splitting of S2.
- However, none of these physical exam findings are sensitive or specific for ACS, and their absence or presence does not rule out or confirm the diagnosis of ACS. Physical examination can be useful to search for other non-cardiac causes of chest pain.

Useful clinical decision rules and calculators

There are two useful systems to help risk stratify patients with ACS.

TIMI risk score

Points	All-cause mortality, new or recurrent MI, or urgent revascularization
0–1	4.7%
2	8.3%
3	13.2%
4	19.9%
5	26.2%
6–7	40.9%

The TIMI risk score is calculated on admission through the sum of seven different variables each with a value of 1 point. The variables are age ≥65 years, ≥3 coronary artery disease risk factors, prior coronary stenosis of ≥50%, ST changes on ECG, ≥2 anginal events in the prior 24 hours, use of aspirin in the last 7 days, and elevated cardiac biomarkers. The TIMI risk score can help to risk stratify patients with NSTE-ACS into lower (<2) and higher (≥2) risk.

GRACE risk model for risk of death in patients with ACS

1. Find points for each predictive factor

Killip class	Points	SBP mmHg	Points	Heart rate	Points	Age	Points	Creatinine (mg/dL)	Points
I	0	≤80	58	<50	0	<30	0	0–0.30	1
II	20	80–99	53	50–69	3	30–39	8	0.40–0.79	4
III	39	100–119	43	70–89	9	40–49	25	0.80–1.19	7
IV	59	120–139	34	90–109	15	50–59	41	1.20–1.59	10
		140–159	24	110–149	24	60–69	58	1.60–1.99	13
		160–199	10	150–199	38	70–79	75	2.00–3.99	21
		≥200	0	≥200	45	80–89	91	≥4.0	28
						≥90	100		

Other risk factors	Points
Cardiac arrest at admission	39
ST segment deviation	28
Elevated cardiac enzyme levels	14

2. Add points for all predictive factors

☐	☐	☐	☐	☐	☐	☐	☐	☐
Killip class	SBP	Heart rate	Age	Creatinine	Cardiac arrest	ST segment	Cardiac enzymes	*TOTAL POINTS*

3. Look up risk of in-hospital mortality corresponding to total points

Points	Mortality (%)	Points	Mortality (%)	Points	Mortality (%)	Points	Mortality (%)
≤60	0.2	110	1.1	160	5.4	210	23
70	0.3	120	1.6	170	7.3	220	29
80	0.4	130	2.1	180	9.8	230	36
90	0.6	140	2.9	190	13	240	44
100	0.8	150	3.9	200	18	≥250	≥52

The GRACE risk model uses a score that is based on eight different parameters ranging from 1 to 372. A nomogram can then be used to extrapolate the risk for in-hospital and post discharge mortality. This risk model is also commonly used to risk stratify patients into low (<109) and high (≥109) risk.

Laboratory diagnosis

List of diagnostic tests

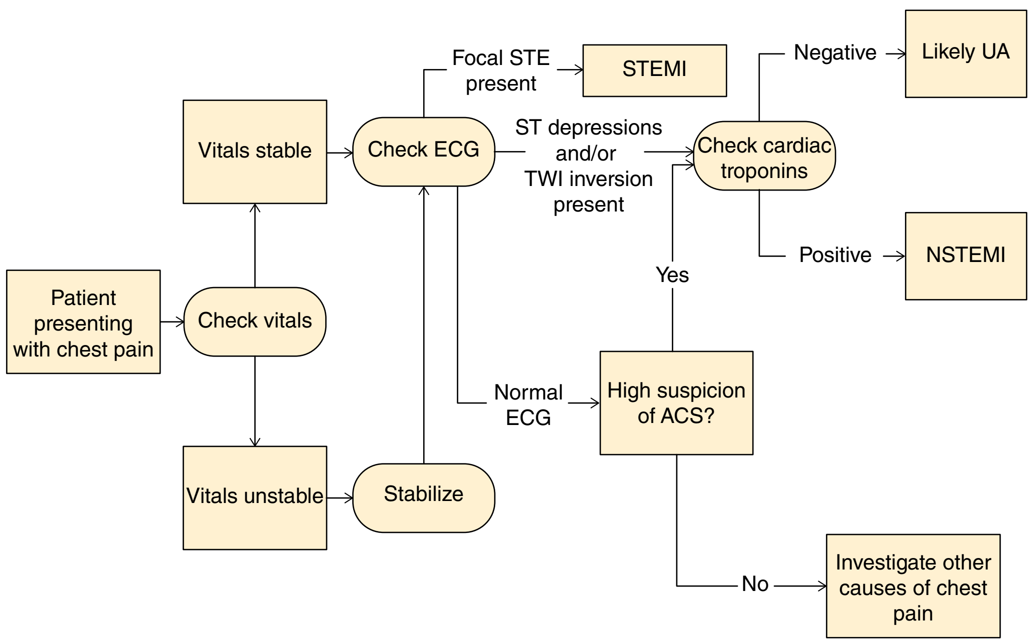
- Cardiac troponins (I and T) are sensitive and specific for diagnosis of myocardial infarction. These biomarkers should be ordered on every patient with suspected ACS, and are typically positive within 2–4 hours of symptoms. Current recommendations are that cardiac troponins should be measured at presentation and again 3–6 hours later. If serial troponins are normal but the ECG and clinical picture are consistent with higher risk ACS, additional troponin levels should be checked after 6 hours.
- Other myocardial biomarkers such as CK-MB and myoglobin are no longer considered necessary as they are less sensitive and specific than cardiac troponins.

List of imaging techniques

- *Electrocardiography (ECG)* is critical in the initial evaluation of patients presenting with suspected ACS and should be performed within the first 10 minutes of arrival. ECG is diagnostic of STEMI when there is ST elevation in two contiguous leads of ≥1 mm in all leads other than leads $V_{2\text{-}3}$. In leads $V_{2\text{-}3}$ STEMI is ≥2 mm of ST elevation in men ≥40 years and ≥2.5 mm in men <40 years; for women the cutoff is ≥1.5 mm in leads $V_{2\text{-}3}$. Other ST changes on ECG should also raise suspicion for MI and can be considered STEMI equivalents. Examples include: new left bundle branch block in the appropriate clinical context; ST depressions in $V_{1\text{-}4}$ can be indicative of a posterior wall MI; and ST depression in multiple leads with ST elevation in aVR may indicate STEMI with a left main or proximal LAD occlusion. Other changes on ECG that may indicate myocardial ischemia include T wave inversions and ST depressions. Deep pathologic Q waves are indicative of an old myocardial infarction. An ECG should be checked every 15–30 minutes within the first hour of presentation and followed serially for evolution.
- *CXR* may be useful in the identification of non-cardiac causes of chest pain such as pneumothorax. It can also help in the identification of aortic dissection if it demonstrates a widened mediastinum. Chest X-rays are commonly ordered on most patients presenting with chest pain.
- *CT angiography of the chest* can be useful in ruling out pulmonary embolism and aortic dissection if those two diagnoses are high on the differential. New data suggest that CT of the coronary arteries may be cost effective in diagnosing or ruling out coronary disease in low risk patients with chest pain.
- *Coronary angiography* is the gold standard for diagnosis of coronary artery disease and allow for intervention. This should be done in all patients with STEMI who present within the first 12–24 hours, with evidence of ongoing ischemia, and in the absence of contraindications. Coronary angiography should also be performed in NSTE-ACS patients who fail ischemic guided therapy as outlined later, or those who are at high risk based on GRACE or TIMI score as outlined earlier.
- *Non-invasive cardiac testing* can be used in patients with low and intermediate risk NSTE-ACS to assess for ischemia and for prognostic purposes. Exercise ECG stress testing can be done in those with unstable angina who are asymptomatic and stable for 12–24 hours, or in NSTEMI after 2–5 days. An ECG exercise stress test is useful in patients who can exercise and have a normal resting ECG. In those with an abnormal resting ECG myocardial perfusion imaging (e.g. thallium stress test) can be conducted, and in those who are unable to exercise a pharmacologic stress test with imaging can be performed.

Diagnostic algorithm (Algorithm 16.1)

Algorithm 16.1 Diagnosis of ACS



Potential pitfalls/common errors regarding the diagnosis of disease

- It is important to consider a broad differential diagnosis when approaching a patient with chest pain. Committing yourself to the diagnosis of ACS without considering other potentially life-threatening causes of chest pain could result in poor outcomes.
- It is not uncommon for patients to present with 'atypical' symptoms, particularly women, the elderly, and diabetics. It is critical to closely consider risk factors for ACS in these patients as it can be harder to identify.

Treatment

Treatment rationale

- ACS is initially treated medically in the same way whether it is STEMI or NSTE-ACS.
- Standard first line treatment is antiplatelet therapy with non-enteric coated aspirin at a dose of 162–325 mg and a P2Y12 inhibitor.
- Anticoagulation is also indicated in either STE- or NSTE-ACS. The cornerstone of management in STEMI is emergent revascularization.
- Current guidelines recommend that patients who present with STEMI, within the first 12–24 hours of symptoms, receive percutaneous coronary intervention (PCI) within 90 minutes of first medical encounter.
- In the event that a patient presents with a STEMI to a non-PCI capable hospital they should be transferred to a PCI capable hospital. In such patients if the anticipated delay from first medical encounter to PCI is >120 minutes they should receive thrombolysis within 30 minutes of first medical contact. They should then be transferred to a PCI capable hospital within 3–24 hours for intervention.
- Patients with NSTE-ACS receive medical therapy as mentioned earlier and are risk stratified using the TIMI or GRACE scoring system. Those who are considered higher risk (TIMI ≥2, or GRACE ≥109) are recommended to undergo early invasive therapy within 24 hours, whereas those who are lower risk are trialed with ischemic-guided therapy.
- In the event that patients who are lower risk fail ischemic-guided therapy they are also sent for PCI.

Table of treatment

Treatment	Comments
Medical treatment *Antiplatelet drugs* • Aspirin 162–325 mg followed by 81 mg daily	Aspirin is the standard first line treatment for all patients with ACS and should be continued indefinitely. In those who cannot tolerate aspirin clopidogrel can be used
P2Y12 inhibitors • Clopidogrel 300–600 mg followed by 75 mg daily • Prasugrel 60 mg followed by 10 mg daily • Ticagrelor 180 mg followed by 90 mg twice daily • Cangrelor: administer IV 30 μg/kg bolus followed by 4 μg/kg/min continuous infusion	A P2Y12 inhibitor should be continued in addition to aspirin for at least 1 year • Clopidogrel has been shown when used with aspirin to be superior to aspirin alone in preventing death and cardiovascular events. Medication should be stopped at least 5 days prior to CABG • Prasugrel has been shown to be an effective P2Y12 inhibitor in combination with aspirin, however with an increased risk of bleeding when compared with clopidogrel. This increased risk was particularly in those patients with prior history of cerebrovascular event, those older than 75 years, and patients with body weight <60 kg. For this reason, prasugrel is contraindicated in these patients. Prasugrel has also been shown to have increased risk of bleeding when given upstream of planned PCI and is thus not indicated for 'upfront' therapy • Ticagrelor has been demonstrated to have superior outcomes compared with clopidogrel. Benefit is only seen in patients taking 75–100 mg of aspirin, thus aspirin 81 mg is recommended in these patients. Dyspnea is a common side effect of ticagrelor but rarely limits its use • Cangrelor is the only IV P2Y12 inhibitor that is currently available. It has been shown to have a significant decrease in periprocedural ischemic events when compared with clopidogrel. Cangrelor may play an important role in bridging patients to CABG given its short half-life
GP IIb/IIIa inhibitors • Eptifibatide IV 180 μg/kg bolus followed by 2 μg/kg/min continuous infusion. • Tirofiban IV loading dose with 25 μg/kg followed by continuous infusion of 0.15 μg/kg/min • Abciximab IV loading dose of 0.25 mg/kg followed by 0.125 mg/kg/min (max. of 10 μg/min) continuous infusion for 12 hours	GP IIb/IIIa inhibitors have strong antiplatelet function and were commonly used in the time before P2Y12 inhibitors and dual antiplatelet therapy were standards of care. Current guidelines recommend their use in NSTEMI at the time of PCI in patients who have not been adequately treated with a P2Y12 inhibitor. Their use is also considered reasonable in patients who have been adequately treated with clopidogrel and are being anticoagulated with heparin at the time of PCI. There are not adequate data at this point to support their use in combination with the newer P2Y12 inhibitors
Anticoagulants • Enoxaparin 1 mg/kg subcutaneously every 12 hours • Bivalirudin IV 0.75 mg/kg bolus prior to procedure followed by 1.75 mg/kg/h continuous infusion • Unfractionated heparin (UFH) 60 IU/kg IV (maximum 4000 IU), followed by initial infusion of 12 IU/kg/h (max. 1000 IU/h)	Anticoagulation is standard of care in all patients with definite ACS, in addition to dual antiplatelet therapy • Enoxaparin has been demonstrated to significantly decrease recurrent ischemic events when compared with UFH, however it has a significantly higher bleeding risk. Given that it is renally cleared it should be avoided in patients with significant renal dysfunction (eGFR <30). Recommended duration is throughout the hospitalization or until PCI is done • Bivalirudin is indicated in patients going for PCI with STEMI, or in patients with NSTE-ACS who are being managed with an early invasive strategy when it can be administered until PCI is performed. It has been demonstrated to be non-inferior when given alone in comparison with UFH or LMW heparin given with a GP IIb/IIIa inhibitor, however with a lower risk of bleeding. Recent data suggest however that UFH may perform better than bivalirudin with no significant increase in bleeding risk

(*Continued*)

(*Continued*)

Treatment	Comments
Medical treatment • Fondaparinux administered as 2.5 mg SC daily	• UFH has been shown in multiple trials to be an effective anticoagulant for use in ACS. UFH is often the anticoagulant of choice in patients with renal dysfunction as it does not require dose adjustment • Fondaparinux has been demonstrated to be effective in the management of NSTE-ACS and is typically given for the duration of the hospitalization or until PCI. Of note it is contraindicated in patients with creatinine clearance <30. Furthermore, if the patient undergoes PCI an additional anticoagulant with anti-IIa activity must be given to prevent catheter thrombosis
Thrombolytics • Alteplase 15 mg, followed by 50 mg over 30 minutes, then 35 mg over 60 minutes • Tenecteplase 40 mg as a single IV push for persons between 70 and 80 kg	Thrombolytics are specifically indicated only for STEMI in the setting of an anticipated delay in primary PCI of over 120 minutes. Use of thrombolytics is specifically contraindicated in the case of NSTE-ACS
Adjunctive medical therapies • Beta-blockers • High intensity statins • ACE inhibitor • Angiotensin receptor blockers	• Beta-blockers have been shown to decrease the likelihood of arrhythmias and reinfarction. Current guidelines recommend that beta-blockers be given within 24 hours to all patients without contraindications such as evidence of cardiogenic shock • High intensity statins are indicated in all patients who present with ACS who do not have a contraindication to receiving treatment • ACE inhibitors are generally recommended to all patients with STEMI with high risk features (previous MI, anterior STEMI, ejection fraction <40%). They should also be given for patients with NSTE-ACS who have reduced ejection fraction (<40%) • Angiotensin receptor blockers are generally second line treatment and used for patients who are unable to tolerate ACE inhibitors
Procedural management Percutaneous coronary intervention (PCI)	Early revascularization with PCI is the cornerstone of management in STEMI and high risk NSTE-ACS. In the case of STEMI, current recommendations are for PCI of the culprit lesion emergently within 90 minutes of presentation to the hospital as described earlier. Current guidelines for NSTE-ACS are for early PCI (within 24 hours) for patients who are high risk or those who fail ischemic directed therapy
Coronary artery bypass grafting (CABG)	CABG is another option available for revascularization. Although more invasive than PCI it has shown a significant benefit over PCI in patients with multivessel or left main disease, complex coronary anatomy, and comorbidities such as diabetes
Complementary management Cardiac rehabilitation	Comprehensive cardiovascular rehabilitation programs help to address risk factors for cardiovascular disease, and encourage healthy lifestyle changes, and are generally recommended to all eligible patients

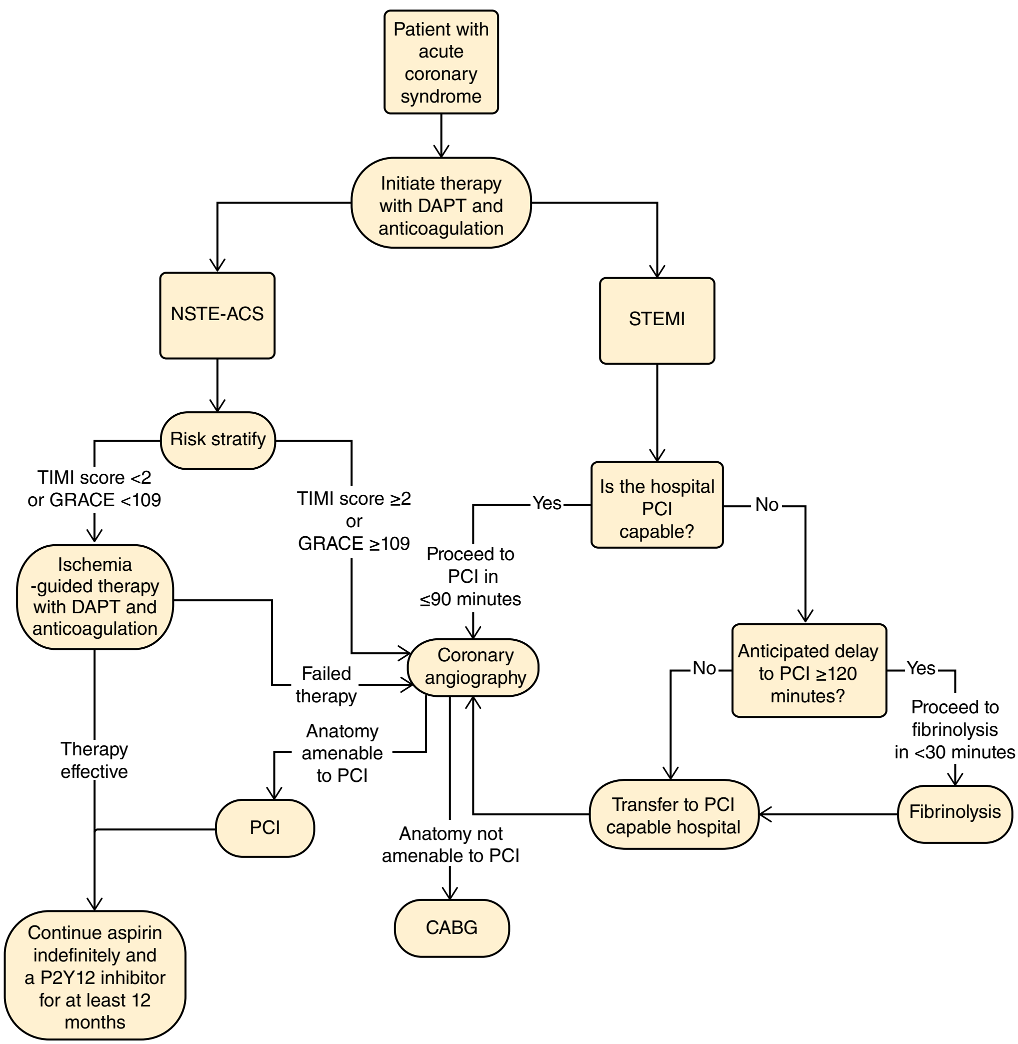
Prevention/management of complications

- Bleeding:
  - All patients should be assessed for bleeding risk. Risk factors include female sex, renal insufficiency, and older age. Anticoagulants and antiplatelet agents should be dosed according to weight when possible and adjusted for renal function to prevent bleeding.

- In the case of minor bleeding, treatment with anticoagulation and antiplatelet therapy should not be interrupted. However, with major bleeding, antiplatelet agents and anticoagulants may need to be stopped and reversed if possible.
- The recommended transfusion goal is a hemoglobin of 8 g/dL in ACS.
- Stroke:
  - Stroke is a known complication of cardiac catheterization and is difficult to manage in the setting of PCI given the risk for intracranial hemorrhage.
  - Limited data exist to suggest that thrombolysis is safe in the setting of stroke after PCI. Therefore, it is of critical importance to consider the risks and benefits of thrombolysis carefully before giving it in the setting of a peri-procedural stroke.

Management/treatment algorithm (Algorithm 16.2)

Algorithm 16.2 Management of ACS



CLINICAL PEARLS

- Medical management of ACS is with anticoagulation and dual antiplatelet therapy (DAPT). This is similar regardless of subtype.
- The key to management of STEMI is emergent PCI to the culprit lesion.
- Risk stratification is critical in the management of NSTE-ACS. Those who are high risk should go for early revascularization, whereas those who are low risk should be trialed with ischemic-guided therapy first.

Special populations

Pregnancy

ACS is rare in pregnant patients. PCI with a bare metal stent is recommended for STEMI and high risk NSTE-ACS to minimize the duration of DAPT. DAPT with clopidogrel and aspirin should be used for the shortest period possible; GP IIb/IIIa inhibitors, prasugrel, and ticagrelor are not recommended.

Elderly

Elderly patients are at higher risk for complications from ACS. Current guidelines recommend that elderly patients (≥75 years old) receive similar benefit from guideline-directed medical therapy as younger patients and thus should be treated similarly. Antiplatelet therapy with prasugrel is contraindicated in patients ≥75 years of age.

Other

ACS patients on anticoagulation are a challenging population to treat. These patients are at high risk for bleeding complications given their need for anticoagulation and DAPT (triple therapy). Current guidelines recommend shortening the duration of triple therapy as much as possible. Strategies to accomplish this include placing a bare metal stent to shorten duration of required DAPT. The evidence in this area is evolving and the interventionalist should be consulted prior to discharge.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Modern therapies have resulted in a significant improvement in the prognosis of ACS.
- STEMI initially has higher short-term mortality rates than NSTE-ACS, however, long-term mortality rates are lower or the same as NSTE-ACS.
- Patients with signs of heart failure on presentation have a significantly worse prognosis.
- In patients with decreased ventricular function, the left ventricular ejection fraction should be rechecked ≥40 days later.

Natural history of untreated disease

Patients with ACS who are not treated promptly can develop a large infarction. Over time the infarcted tissue is replaced by scar and the left ventricle undergoes remodeling. The end result is eccentric hypertrophy and progressively worsening systolic dysfunction leading to heart failure.

Prognosis for treated patients

- In-hospital mortality for patients with STEMI is higher than for NSTE-ACS (5.5% versus 3.9%). However, long-term outcomes suggest that mortality rates are worse for NSTEMI (1 year mortality rate of 10% for NSTEMI versus 6.5% for STEMI).
- This is thought to be due to the fact that patients with NSTE-ACS tend to be older, have multivessel disease, and more comorbidities. Patients with ACS who present with heart failure have a significantly higher in-hospital and 6 month mortality rate compared with those who present without heart failure (20.7% versus 5.9%).

Follow-up tests and monitoring

- All patients who present with ACS should have an initial evaluation of left ventricular ejection fraction (LVEF) as this will change medical management, and helps to identify patients who are at risk for sudden cardiac death.
- In those with decreased left ventricular function it is recommended that follow-up evaluation of LVEF be performed after 40 or more days to assess for recovery of systolic function after revascularization or medical therapy. Patients with persistently reduced LVEF can benefit from an implantable cardioverter defibrillator to prevent sudden cardiac death. Certain high risk patients (very poor LV function, frequent ventricular ectopy) may need to be discharged with a wearable cardioverter-defibrillator. An EP consult should be obtained prior to discharging such patients.

Reading list

Alexander JH, Smith PK. Coronary-artery bypass grafting. N Engl J Med 2016;374:1954–64.

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Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114(12):1852–66.

Bhatt DL, Hulot JS, Moliterno DJ, Harrington RA. Antiplatelet and anticoagulation therapy for acute coronary syndromes. Circ Res 2014;114(12):1929–43.

Chang M, et al. TCTAP A-028 coronary artery bypass surgery versus drug-eluting stent implantation for non-ST-elevation acute coronary syndrome: analysis of pooled data from the BEST, PRECOMBAT and SYNTAX Trials. J Am Coll Cardiol 2016;67(16):S12.

Eisen A, Giugliano RP, Braunwald E. Updates on acute coronary syndrome: a review. JAMA Cardiol 2016;1(6):718–30.

Kar S, Bhatt DL. Anticoagulants for the treatment of acute coronary syndrome in the era of new oral agents. Coron Artery Dis 2012;23(6):380–90.

Levine GN, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012. ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart. Circulation 2016;134(10):123–55.

Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368(21):2004–13.

SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–16.

Steg PG, et al.; Global Registry of Acute Coronary Events (GRACE) Investigators. Determinants and prognostic impact of heart failure complicating acute coronary syndromes observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004;109(4):494–9.

Suggested websites

https://www.outcomes-umassmed.org/grace.
http://www.timi.org/index.php?page=calculators.
http://tools.acc.org/ASCVD-Risk-Estimator/.

Guidelines

National society guidelines

Title	Source and comment	Date and reference
2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes	AHA/ACC Most current US clinical practice guidelines available for the management of NSTE-ACS	2014 J Am Coll Cardiol Amsterdam EA, et al. J Am Coll Cardiol 2014;64(24):e139–228
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction	ACCF/AHA Most recent US clinical practice guidelines available for the management of STEMI	2013 O'Gara PT, et al. J Am Coll Cardiol 2013;61(4):e78–140

International society guidelines

Title	Source and comments	Date and reference
2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation	ESC Current European clinical practice guidelines for the management of NSTE-ACS	2015 Roffi M, et al. Eur Heart J 2016;37(3):267–315
ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation	ESC Current European clinical practices guidelines for the management of STEMI	2012 Steg PG, et al. Eur Heart J 2012;33(20):2569–619

Evidence

Type of evidence	Title and comment	Date and reference
RCT	*PLATO trial* Patients with ACS were randomized to receive either clopidogrel and aspirin or ticagrelor and aspirin. Patients in the ticagrelor group had significantly lower rates of primary composite outcome (death from vascular causes, MI, or stroke) without any increased risk of bleeding	2009 Wallentin L, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361(11):1045–57
RCT	*CURE trial* Patients with NSTE-ACS were randomized to receive either clopidogrel and aspirin or placebo and aspirin. Patients who received clopidogrel had significantly better primary composite outcome (death from cardiovascular causes, non-fatal MI, or stroke), however with significantly increased risk of major bleeding	2001 Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345: 494–502
RCT	*OASIS-5 trial* Patients with NSTE-ACS were randomized to receive fondaparinux or enoxaparin for anticoagulation. Fondaparinux was found to be non-inferior to enoxaparin with significantly decreased major bleeding rates. However, fondaparinux had a significantly higher incidence of catheter thrombosis, leading to the recommendation that in those patients undergoing PCI who receive fondaparinux, an additional anticoagulant with anti-IIa activity must be given	2006 Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354:1464–76
RCT	*TRITON-TIMI 38 trial* Patients with ACS were randomized to receive aspirin and clopidogrel or aspirin and prasugrel. Patients in the prasugrel arm had significantly decreased rates of primary composite endpoint (cardiovascular death, non-fatal MI, and non-fatal stroke). However, there was a significantly increased risk of bleeding particularly in patients >75 years of age, <60 kg, or with history of previous CVA	2007 Wiviott SD, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357(20):2001–15

Type of evidence	Title and comment	Date and reference
RCT	*ACUITY trial* Patients with NSTE-ACS were randomized to receive heparin (UFH or LMWH) with a GP IIb/IIIa inhibitor, bivalirudin with a GP IIb/IIIa inhibitor, or bivalirudin alone. Bivalirudin alone was found to be non-inferior to heparin with a GP IIb/IIIa inhibitor in the ischemic endpoint (death from any cause, MI, or unplanned revascularization). Bivalirudin alone was found to have significantly lower risk of bleeding than heparin with a GP IIb/IIIa inhibitor, thus has a net clinical benefit	2006 Stone GW, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355(21):2203–16
RCT	*CHAMPION-PHOENIX trial* Patients with ACS were randomized to receive clopidogrel and aspirin or cangrelor and aspirin. Patients in the cangrelor arm had reduced incidence of the primary composite outcome (death, MI, unplanned revascularization or stent thrombosis in the first 48 hours)	2013 Bhatt DL, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368(14):1303–13
RCT	*SYNERGY trial* Patients with high risk NSTE-ACS who received PCI were randomized to receive enoxaparin or UFH for anticoagulation. There was no significant difference in the primary endpoint between the two groups, however there was a significantly higher risk of bleeding in the enoxaparin group	2004 Ferguson JJ, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292(1):45–54
RCT	*SYNTAX trial* Patients with severe triple vessel or left main coronary artery disease were randomized to either PCI or CABG. Patients undergoing CABG had a significantly lower primary outcome (death, stroke, MI, or repeat revascularization). This was particularly true for patients with more complex anatomy (SYNTAX score ≥33)	2009 Serruys PW, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360(10):961–72
RCT	*ACCOAST trial* Patients with NSTE-ACS were randomized to receive pretreatment with prasugrel prior to PCI or placebo prior to PCI and prasugrel at the time of PCI. This study found no significant difference in major primary composite outcomes between the two groups, however the pre-treatment group had significantly higher rates of bleeding	2013 Montalescot G, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369(11):999–1010
RCT	*ESSENCE trial* Patients with NSTE-ACS were randomized to receive enoxaparin or UFH. Patients who received enoxaparin had significantly reduced composite outcome (death, MI, or recurrent angina at 14 days, 30 days, and even 1 year out)	2000 Goodman SG, et al. Randomized trial of low molecular weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease: one-year results of the ESSENCE study. J Am Coll Cardiol 2000;36(3):693–8
RCT	*HEAT-PPCI trial* Patients with ACS presenting for primary PCI at a single center were randomized to receive UFH or bivalirudin; the use of GP IIb/IIIa inhibitors was similar between both groups. Patients treated with UFH had significantly lower rates of major cardiac events compared to bivalirudin with no increased risk of bleeding	2014 Shahzad A, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;384(9957):1849–58

Images

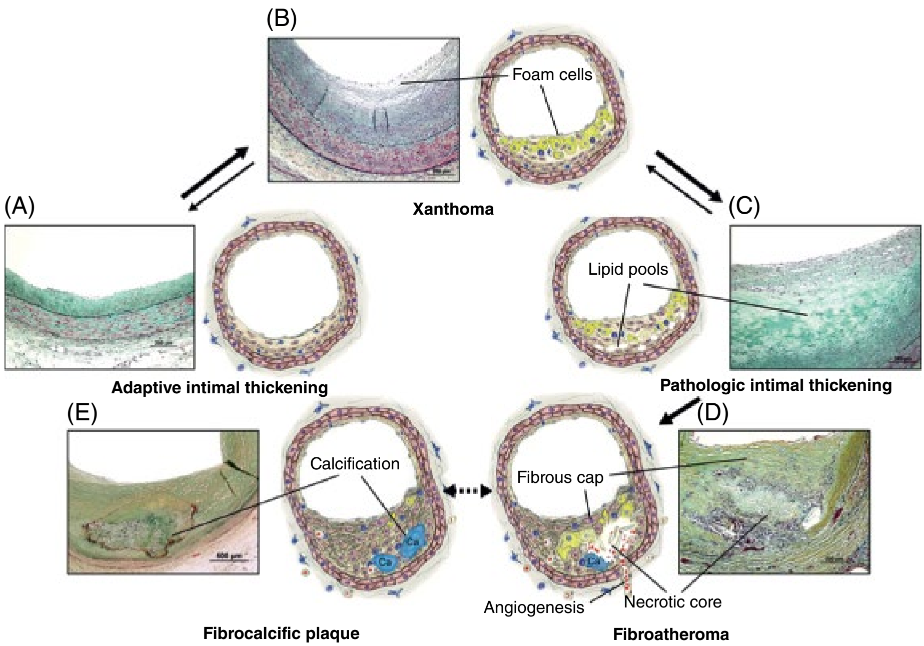

Figure 16.1 Atheromatous plaque formation. (A) LDL particles migrate into the intima of the vessel wall resulting in inflammation and intimal thickening. (B) Monocytes migrate into the intima and differentiate into macrophages, which scavenge LDL molecules, becoming foam cells and forming a xanthoma. (C) Extracellular lipid pools develop. (D) Foam cells undergo apoptosis, forming a necrotic core. (E) Chronic inflammation within the intima eventually results in fibrosis and calcification of the plaque. (See website for color version.)

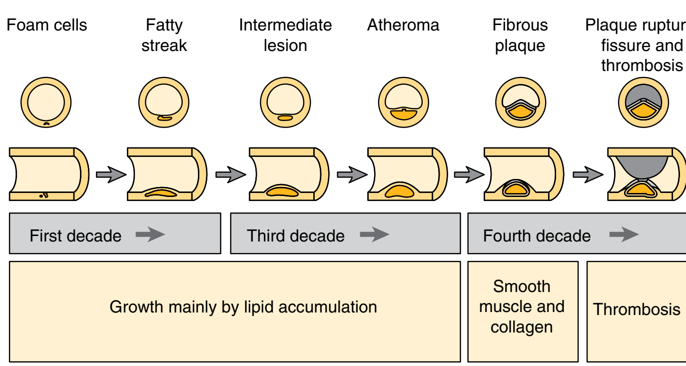

Figure 16.2 Development of coronary artery plaque. Plaques with a thin fibrous cap and large necrotic core are higher risk for plaque rupture. When the plaque ruptures blood is exposed to the thrombogenic material in the core, causing activation of the clotting cascade, platelet aggregation, and thrombus formation. When the thrombus is near-total or totally occlusive, mural infarction occurs resulting in STEMI. When the thrombus is not totally occlusive or dynamic the result is NSTE-ACS.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.
The following image is available in color: Figure 16.1.

with website

CHAPTER 17

Heart Failure Management

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OVERALL BOTTOM LINE

- Heart failure is characterized by impaired cardiac function that can lead to symptoms of congestion and/or hypoperfusion.
- There are many causes for heart failure and acute decompensation. Careful consideration of the underlying precipitant is crucial in the initial management to allow for targeted intervention.
- Characterization of the patient's hemodynamic profile guides acute treatment strategies and provides prognostic guidance.
- Initiation and titration of chronic heart failure therapy with neurohormonal antagonists is necessary to improve outcomes longitudinally.
- Identification of end-stage patients with a poor prognosis should prompt early referral to a heart failure specialist for consideration of advanced therapies.

Background

Definition of disease

- Heart failure is a clinical syndrome of impaired myocardial function where the heart is unable to meet the metabolic demands of the body.
- This syndrome can occur from a variety of initial insults to the heart, but the disease generally progresses over time with progressive negative remodeling of the heart unless the initial insult is temporary or reversible.

Disease classification

- Heart failure can be seen in patients with both preserved ejection fraction and reduced ejection fraction. Distinguishing these two entities is essential to determining appropriate treatment
- The ACA/AHA classifies the progression and severity of disease into four stages:

ACC/AHA stages of heart failure	
A	At high risk for heart failure without structural heart disease
B	Structural heart disease without symptoms of heart failure
C	Structural heart disease with current or prior symptoms
D	Refractory heart failure requiring specialized intervention

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Incidence/prevalence

- An estimated 5 million Americans are living with heart failure and the prevalence is expected to increase 25% by 2030.
- Approximately half of these patients have preserved ventricular function.

Etiology

- Diastolic heart failure (HFpEF) is typically associated with long-standing hypertension in an older and predominantly female population. Comorbid conditions of obesity, coronary artery disease, and diabetes are often present. Apart from this classic phenotype, diastolic dysfunction can also be seen in diseases including hypertrophic cardiomyopathy and infiltrative, pericardial, and valvular diseases.
- Systolic heart failure occurs as a result of a variety of insults. Broadly, there are ischemic and non-ischemic causes to heart failure:
  - Ischemic heart failure results from reduced myocardial perfusion from the coronary arteries. Usually this is from underlying coronary artery disease, but can also be seen from coronary emboli or dissection.
  - Non-ischemic causes of heart failure can be idiopathic or associated with a broad differential of diseases. These include, but are not limited to, infectious, hereditary, valvular, autoimmune, and infiltrative causes, toxin exposure, arrhythmias, and nutritional deficiencies.

Pathology/pathogenesis

- After initial myocardial injury, chronic systolic heart failure is associated with progressive ventricular remodeling due to neurohormonal activation; notably the sympathetic nervous system and renin angiotensin system. This activation causes worsening of ventricular function and disease progression over time and is an important target of medical therapy.
- Diastolic heart failure is less well defined. Increased diastolic filling pressures are required to maintain cardiac performance. The mechanisms contributing to ventricular dysfunction despite preserved systolic function include microvascular disease, adverse ventricular hypertrophy, and remodeling.

Prevention

There are many potential causes of heart failure. However, treatment of the major risk factors associated with heart failure development (see Primary Prevention section) reduces the likelihood of the development of heart failure.

Screening

- Although patients can have asymptomatic ventricular dysfunction, the ACC/AHA guidelines currently do not recommend periodic screening of ventricular function. However, screening patients at highest risk of cardiac dysfunction (i.e. patient on cardiotoxic medications) is performed in usual clinical practice.
- Beyond monitoring of ventricular function, measurement of myocardial changes with strain imaging can detect early cardiotoxicity in patients receiving cancer therapies.
- B-type natriuretic peptide (BNP) is a useful biomarker that is elevated in patients with asymptomatic left ventricular dysfunction and has been shown to be a cost effective screening tool.

Primary prevention

- Hypertension control.
- Diabetes mellitus management.
- Dyslipidemia management.
- Avoidance of excessive alcohol intake.
- Tobacco cessation.
- Restriction of sodium intake.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Patients with symptomatic heart failure will present with symptoms of congestion as well as features of low perfusion in advanced disease.
- On physical exam, close attention should be paid to the presence of an elevated jugular venous pressure. Other features are less accurate. Poor perfusion can be manifest by the presence of cool extremities, hypotension, and tachycardia.
- Initial investigation should include laboratory investigations to support the diagnosis of heart failure (such as BNP), evaluation for the presence of end-organ dysfunction, and screening for possible underlying diseases that cause cardiac dysfunction.
- CXR, electrocardiogram, and echocardiography are necessary first steps that can confirm the diagnosis as well as providing information on the underlying cause of decompensation. Mode of evaluation for underlying coronary disease should be based on clinical suspicion. Selected patients may benefit from MRI, right heart catheterization, and endomyocardial biopsy.

Differential diagnosis of causes of decompensated heart failure

Category	Examples
Ischemia	Coronary artery disease, coronary emboli, dissection
Arrhythmias	Tachyarrhythmia, conduction abnormalities, bradycardia
Myocarditis	Viral, HIV, autoimmune
Medications	NSAIDs, calcium channel blockers, anthracyclines, substance abuse
Non-compliance	Dietary and medical adherence; risk factor control
Infiltrative	Amyloid, sarcoid, hemochromatosis, Fabry's
Metabolic	Thyroid disease, diabetes, pheochromocytoma, anemia, obesity
Valvular disease	Mitral regurgitation, aortic regurgitation, aortic stenosis
Nutritional	Thiamine, carnitine, selenium
Miscellaneous	Takotsubo cardiomyopathy, hereditary diseases, hypertrophic, congenital, ventricular non-compaction, peri-partum cardiomyopathy

Typical presentation

Although patients can present with asymptomatic ventricular dysfunction, most patients present with signs and symptoms of congestion and/or hypoperfusion. This includes worsening dyspnea on exertion, weight gain, and fatigue. The acuity of the presentation will depend on the mechanism of myocardial injury. For example, a patient with heart failure after an acute myocardial infarction may present with dyspnea increasing over hours or days without significant weight gain or edema. Evidence of hypoperfusion is less common, but is associated with a worse prognosis.

Clinical diagnosis

History

- The goal of the clinician when assessing a patient with heart failure is to determine their hemodynamic profile and identify any reversible conditions that contribute to the decompensation. The hemodynamic profile allows the clinician to categorize the patient in one of four categories based on the presence or absence of congestion and perfusion.

- Evidence of congestion by history can be observed by symptoms due to elevated cardiac filling pressures. Elevated left-sided filling pressures will manifest with symptoms due to pulmonary edema such as dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea. Elevated right-sided pressures may manifest with abdominal distension or lower extremity edema.
- Evidence of hypoperfusion may include any symptom of poor end-organ function such as dizziness, lethargy, or oliguria.
- The precipitant and etiology of heart failure can also be detected by a careful history. Although ischemia is a common and necessary precipitant to consider by history, a wide differential needs to be considered.

Physical examination

- No feature of congestion on physical examination should be used in isolation to confirm or exclude the presence of heart failure. Jugular venous distention is not only limited by clinician expertise, but can also be elevated in other conditions including pulmonary embolism, acute myocardial infarction, and isolated right ventricular failure. The presence of rales or lower extremity edema are commonly considered by clinicians, however they can be absent in patients with decompensated heart failure.
- Assessment of hypoperfusion begins with the evaluation of the blood pressure and heart rate. Hypotension and tachycardia are important markers of morbidity and mortality with important associated treatment options. The presence of cool extremities on examination is an important manifestation of hypoperfusion.

Estimating disease severity and prognosis

- NYHA functional class has traditionally been used with demonstrated prognostic power as well as providing help in determining longitudinal response to therapy. However, this scale has many limitations. It has significant inter-user variability, may change day to day, and is not a sensitive marker of patients at highest risk of mortality.

NYHA class	Symptoms
I	Asymptomatic. No limitation in physical activity
II	Limitations with ordinary activity
III	Limitations with less than ordinary activity
IV	Symptomatic at rest. Unable to perform activity

- There are multiple individual factors that can be used to predict survival in heart failure, but no single factor is sufficient to define the risk in an individual patient. Multiple composite scores have been validated to provide a more comprehensive assessment of disease severity and risk stratification. The Seattle Heart Failure Model and Heart Failure Survival Scores are prospectively validated multivariable models that help predict long-term survival.

Laboratory diagnosis

List of diagnostic tests

- Routine testing includes serum electrolytes, creatinine, liver function, complete blood count, troponin, venous lactate, and lipid profile.
- Screening for thyroid disease, HIV, and hemochromatosis is reasonable in all patients to exclude potential causes of new onset or unexplained heart failure. Testing for diseases such as autoimmune disorders, pheochromocytoma, nutritional deficiency screening, or amyloidosis is reasonable if there is clinical suspicion.
- BNP is most useful to screen for heart failure in a patient with unexplained dyspnea. It can also be useful as a marker of disease severity.

List of imaging techniques

- A CXR is appropriate in all patients with acute decompensation of heart failure (Figure 17.1).
- An ECG is appropriate in all patients to evaluate for arrhythmias, as well as to suggest the presence of ischemia or prior infarction. An ECG with low voltage despite the presence of left ventricular hypertrophy on echocardiography should raise suspicion for infiltrative disease such as amyloidosis. Conduction abnormalities can be seen in myocardial infarction, myocarditis, Lyme disease, and sarcoidosis.
- Transthoracic echocardiography is appropriate in all new diagnoses of heart failure and in patients with unexplained decompensation. This provides useful information in differentiating preserved and reduced ejection fraction phenotypes as well as providing information on the etiology of heart failure.
- Assessment of underlying coronary disease can be done by multiple testing modalities. Patients with high likelihood of coronary disease, particularly those with symptoms of angina, should be evaluated by coronary angiography. Cardiac CT angiography is an acceptable alternative to exclude an ischemic etiology of heart failure. Stress testing by nuclear imaging or echocardiography can be used in patients with low suspicion for coronary disease.
- MRI can be useful to evaluate patients with unexplained heart failure. Diseases including hemochromatosis, hypertrophic cardiomyopathy, infiltrative diseases, sarcoidosis, and myocarditis can be suggested by MRI findings.
- Right heart catheterization is not recommended for routine use in patients with decompensated heart failure. It should be considered in patients who have an uncertain hemodynamic profile and to manage patients with cardiogenic shock.
- Endomyocardial biopsy is used in patients with rapid decompensation to exclude a steroid responsive condition such as giant cell myocarditis. It can also be used to confirm infiltrative disease such as cardiac amyloidosis.

Potential pitfalls/common errors made regarding diagnosis of disease

- The hemodynamic profile may be difficult to determine in many patients, particularly young patients. They can often present without lower extremity edema, normal lung auscultation, and lower NYHA class despite advanced underlying disease.
- BNP can be an inaccurate assessment of heart failure in several conditions. It can be elevated in patients with chronic renal disease. Conditions such as advanced age and obesity can lower the BNP level despite the presence of underlying heart failure.

Treatment

Treatment rationale

- The aim of therapy is to quickly relieve symptoms, optimize the hemodynamic profile, manage reversible conditions which may be responsible for decompensation, and initiate long-term medical therapy.
- Characterization of the patient into a particular hemodynamic profile helps guide initial therapy.
- Diuretics are the mainstay of medical therapy in patients with congestive symptoms. Dosing needs to be individualized. Initial high dose intravenous diuretics can generally be safely given to patients to rapidly improve symptoms in patients on chronic oral diuretic therapy.
- Vasodilator therapy is less frequently used in clinical practice, but can rapidly improve symptoms in patients without hypotension ('warm and wet'). Vasodilators (nitroglycerin, nitroprusside, nesiritide) reduce the afterload on the heart with subsequent improvement in pulmonary congestion (Table 17.1).
- Supplemental oxygen and non-invasive positive pressure ventilation can also be used to relieve dyspnea in conjunction with vasodilator and diuretic therapy. Non-invasive positive pressure ventilation should be avoided in patients with hypotension, vomiting, pneumothorax, and poor mental status.

Table 17.1 Vasoactive medications.

Agent	Dose	Mechanism	Inotropy	CO	SVR	MAP
Milrinone	0.375–0.75 μg/kg/min	PDE-3 inhibitor	↑	↑↑	↓↓	↓
Dobutamine	1–10 μg/kg/min	B-1, B-2, α-1	↑↑	↑↑	↓	≈
Dopamine	1–3 μg/kg/min	Dopamine-1	≈	≈	↓	↓
	3–10 μg/kg/min	B-1 > α-1	↑	↑	↑	↑
	10–20 μg/kg/min	B-1 < α-1	↑	↑	↑↑	↑↑
Epinephrine	2–10 μg/kg/min	B-1, B-2, α-1	↑↑	↑↑	↑↑	↑↑
Norepinephrine	2–10 μg/kg/min	B-1, α-1	↑↑	↑↑	↑↑	↑↑
Nitroprusside	0.3–5 μg/kg/min	Nitric oxide	≈	↑	↓↓	↓
Nitroglycerin	10–200 μg/kg/min	Nitric oxide	≈	↑	↓↓	↓
Nesiritide	0.015–0.03 μg/kg/min	BNP	≈	↑	↓↓	↓

α, alpha-adrenergic agonist; B, beta-adrenergic agonist; BNP, B-type natriuretic peptide.

- Inotropic or mechanical support is used in patients with evidence of hypoperfusion with elevated filling pressure ('cold and wet') until the hemodynamic condition is corrected. There are several intravenous agents that can be used for inotropy. Except for cases of profound shock, dobutamine or milrinone are typical first line agents. These agents are continued until the hemodynamic profile is reversed. Mechanical support should be considered in refractory cases.
- Although less common, patients who are 'cold and dry' will require inotropic or mechanical support while a reversible cause is identified. If no reversible cause is noted, these patients need early consideration of mechanical support or cardiac transplantation evaluation.
- After stabilization of the patient's hemodynamic profile and management of any precipitant of decompensation, patients with systolic heart failure should be initiated on chronic heart failure therapy prior to discharge. Neuro-hormonal antagonists such as beta-blockade, RAAS blockade, and aldosterone antagonists are essential to prevent further ventricular remodeling and decompensation. Treatment of diastolic heart failure largely focuses on management of associated hypertension and volume control with diuretic therapy.

When to refer

The acutely hospitalized patient provides an opportunity to assess their overall prognosis and determine if referral to an advanced heart failure specialist is indicated. The following patients are appropriate for referral:

- Patients with cardiogenic shock are appropriate for early referral, particularly prior to the development of irreversible multiorgan failure.
- Patients who require inotropic support and are unable to be weaned despite correction of the hemodynamic profile.
- Patients with intolerance to neurohormonal blockade, particularly due to hypotension or renal failure.
- Patients with recurrent hospitalizations for heart failure despite optimal medical therapy.

Prevention/management of complications

Diuretic dosing is often associated with or limited by worsening renal failure. If the patient is developing renal failure with diuresis, it is first important to confirm that the suspected hemodynamic profile is correct. If there is uncertainty, consider right heart catheterization. If there is evidence of hypoperfusion, empiric use of vasodilators or inotropic support can be considered.

Table of treatment for acute heart failure

	Warm	Cold
Dry	Normal cardiac output Normal systemic vascular resistance Normal PCWP Rx: Titration of guideline directed therapy	Low cardiac output High systemic vascular resistance Normal PCWP Rx: Inotropes
Wet	Normal cardiac output Normal systemic vascular resistance High PCWP Rx: Diuresis +/– vasodilators	Low cardiac output High systemic vascular resistance High PCWP Rx: Inotropic support and diuresis

CLINICAL PEARLS

- Treatment should be targeted based on the suspected hemodynamic profile.
- Identify reversible conditions that may be contributing to decompensation.
- If patient is not responding to initial therapy, reassess hemodynamic profile and consider right heart catheterization.
- Early referral for advanced heart failure management in patients with recurrent hospitalizations, inotropic dependence, or shock. Refer before the development of irreversible end-organ damage.
- After stabilization of hemodynamic profile, transition patient to chronic heart failure therapy with education and close follow-up to prevent worsening heart failure and re-hospitalization.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Recurrent hospitalization is a strong predictor of mortality.
- Patients with neuro-hormonal intolerance, especially due to hypotension and renal failure, suggest advanced disease warranting referral to a heart failure specialist.
- Consider use of predictive models to help define long-term risk of death in heart failure patients.

Follow-up tests and monitoring

- Patients after heart failure hospitalization benefit from early and close follow-up post discharge. A phone call 3 days after discharge and in person follow-up in 1–2 weeks is appropriate.
- Patients should be educated on disease progression, symptoms of worsening heart failure, role of medical therapy, physical activity, and dietary modification.
- Titration of neurohormonal blockade and monitoring of response to medical therapy requires close longitudinal follow-up.

Reading list

Fonarow GC, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005;293(5):572–80.

Fonarow GC, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Internal Med 2008;168(8):847–54.

Go AS, et al. Heart disease and stroke statistics. Circulation 2013;127(1):e6–245.

Nohria A, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41(10):1797–804.

Reynold HR, et al. Cardiogenic shock: current concepts and improving outcomes. Circulation 2008;117(5):686–97.
Ronco C, et al. Cardiorenal syndrome. J Am Coll Cardiol 2008;52(19):1527–39.
Westaby S, et al. Cardiogenic shock in ACS. Part 1: prediction, presentation and medical therapy. Nature Rev Cardiol 2012;9:158–71.

Suggested websites

https://depts.washington.edu/shfm/
www.pvloops.com (requires purchase of app)

Guidelines

National society guidelines

Title	Source	Date and reference
Guideline for the Management of Heart Failure. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines	American College of Cardiology Foundation/ American Heart Association	2013 Yancy CW, et al. Circulation 2013;128:e240–327

Evidence

Type of evidence	Title and comment	Date and reference
RCT	*ESCAPE trial* Randomized trial of 433 patients to pulmonary artery catheter guided therapy. Did not affect overall mortality and hospitalization	2005 Stevenson LW, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness. JAMA 2005;294(13):1625–33
RCT	*DOSE trial* Randomized to continuous versus intermittent dosing of Lasix. No benefit seen to continuous infusion, higher dosing (2.5× total oral dose) trended with better symptom relief	2011 Felker GM, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364(9):797–805
RCT	*ASCEND trial* Randomization to nesiritide had a trend in improvement in symptoms with increased rate of hypotension and no change in 30 day outcomes	2011 O'Connor CM, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365(1):32–43
RCT	*SHOCK trial* Early revascularization in patients with cardiogenic shock with myocardial infarction improved 6 month mortality	2006 Hochman JS. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295(21):2511–15

Image

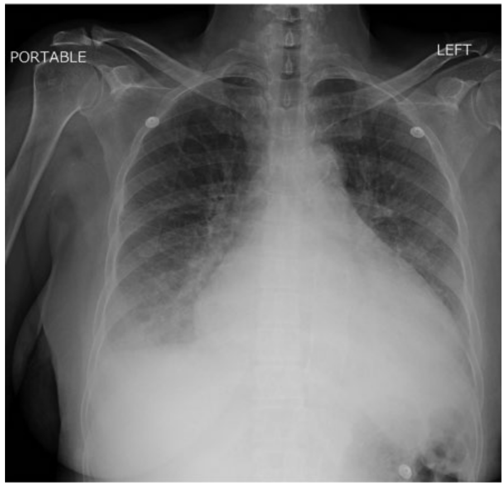

Figure 17.1 Chest radiograph of a patient with cardiomegaly and pulmonary vascular congestion due to acute decompensated heart failure.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 18

Shock Syndromes

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OVERALL BOTTOM LINE

- Development of the syndrome of shock involving multiorgan failure sets off the final downward spiral of a patient towards death. The cornerstone of pathophysiology is decreased oxygen supply and utilization by the cells.
- Early diagnosis and intervention is the key to reducing mortality in circulatory shock.
- Shock syndromes carry an unacceptably high mortality rate even with modern treatment for the multitude of etiologies that can lead to circulatory collapse.
- Clinician's vigilance is the cornerstone for early identification of shock state and the diagnosis of such a state is a clinical diagnosis.
- Awareness of the most common pitfalls as well as early identification and institution of appropriate intervention can prevent the final downward spiral of shock to death.

Background

Definition of disease

- Shock syndrome is a condition that the European Society of Intensive Care Medicine (ESICM) defines as 'generalized acute circulatory failure which is life threatening and is associated with inadequate oxygen utilization by cells.'
- It is the final pathway of a state of cellular dysfunction where the circulation is unable to meet the demands of the tissues, resulting in cellular dysoxia, i.e. mismatch between oxygen delivery and oxygen consumption, resulting in increased blood lactate levels.

Disease classification

- Shock syndromes are divided into four major groupings (hypovolemic, cardiogenic, distributive, and obstructive) along with the underlying diseases that cause each particular type of shock (see Differential diagnosis section).
- It should be emphasized that despite this classification, circulatory collapse resulting in shock generally has overlapping pathophysiology. For example, hypovolemia can be found in cardiogenic shock or in septic (distributive) shock.

Incidence/prevalence

- Circulatory shock accounts for one-third of patients admitted to ICUs in the USA.
- In the SOAP II trial (n = 1679), septic shock accounted for 62.2% (according to the ESICM, reported incidence of septic shock in patients admitted to the ICU varies between 6.3% and 14.7%). Cardiogenic

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shock accounted for 16.7%, hypovolemia accounted for 15.7%, and the rest were accounted for by other distributive and obstructive etiologies.
- 4.6% of ACS patients admitted to the hospital developed cardiogenic shock according to an observational study of 65 119 patients hospitalized.

Etiology

- Circulatory failure or shock is a syndrome that is the final pathway for several etiological conditions that lead to circulatory collapse.
- While circulatory shock is generally divided into four types (hypovolemic, cardiogenic, distributive, and obstructive), the conditions that contribute to development of any of these specific type are multitude as described in the Differential diagnosis section (Figure 18.1).

Pathology/pathogenesis

- The underlying pathologic derangement in shock syndrome is a mismatch between global oxygen delivery (DO_2) and oxygen consumption (VO_2).
- DO_2 is responsive to changes in any of the three components of DO_2 (cardiac output, Hb, and oxygenation) and VO_2.
- In the presence of adequate oxygenation and Hb, cardiac output drives DO_2 to match VO_2.
- The normal DO_2:VO_2 ratio is 5:1 and is achieved by increasing cardiac output (CO) in response to increased demand from cellular respiration (consumption drives delivery) and at this ratio cellular respiration is not supply dependent.
- When the ratio falls below 2:1, cellular respiration becomes supply dependent. This 2:1 ratio corresponds to maximal oxygen extraction by tissues and is the critical level at which tissue hypoxia (oxygen debt) results in anaerobic tissue metabolism leading to acidosis and lactic acid formation, hence elevated blood lactic acid levels.
- Therefore, correction of DO_2 by improving CO should improve survival from shock.
- However, this is not the case as other regional and microcirculatory hemodynamic alterations become active in due course when restoration of DO_2 is delayed.
- Compensatory mechanisms that include extrinsic (autonomic nervous system and circulating norepinephrine from adrenals) and intrinsic (arteriolar and endothelium mediated) regional and microcirculatory autoregulation become overwhelmed with delay in treatment, resulting in systemic inflammatory response syndrome (SIRS). SIRS results in regional flow heterogeneity with shunting of blood supply to non-critical areas of the body.
- As shock state progresses, microcirculatory blood flow, microcirculatory oxygen diffusion, and microcirculatory oxygen utilization become ineffective resulting in microcirculatory failure. At this stage, even if the DO_2 is re-established with adequate CO, the downward spiral and the development of multiorgan dysfunction syndrome (MODS) is inevitable. At this point the patient may continue to decline even with adequate CO.
- If measures to prevent this downward spiral are unsuccessful, death ensues.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Shock syndrome is a clinical diagnosis.
- Early recognition of the development of shock by proactive clinical vigilance is the only preventable measure.

Screening

- Critically ill patients are especially at risk for developing shock syndrome. Studies have shown that the shock syndrome is prevalent in approximately one-third of patients admitted to ICU.
- Critically ill patients should be routinely screened for the development of shock syndrome.
- Screening involves monitoring and evaluating clinical, hemodynamic, and biochemical parameters.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Diagnosis of inadequate tissue perfusion involves looking at clinical, hemodynamic and biochemical variables.
- Clinically, inadequate tissue perfusion can be assessed via the skin (evidence of decreased cutaneous perfusion), kidneys (decreased urine output <0.5 mL/kg/h), and brain (altered mental status).
- Hemodynamically, reliance on hypotension (SBP <90 mmHg or MAP <65 mmHg or a reduction of >40 mmHg from baseline) alone to define shock should be avoided. However, frequent measurement of blood pressure, heart rate, respiratory rate, temperature, and other variables listed should be carried out.
- Biochemically, blood lactate levels (>2 mEq/L or >2 mmol/L) are useful in detecting mismatch in tissue oxygen delivery and demand, while keeping in mind that there are other conditions that may result in increased lactate levels without the presence of such a mismatch.
- Routinely screen patients at risk using this information to detect impending shock so that early intervention can be instituted.

Differential diagnosis

Differential diagnosiss

Hypovolemic

- Hemorrhagic:
  - Trauma
  - Gastrointestinal
  - Retroperitoneal
- Non-hemorrhagic:
  - External fluid loss
  - Dehydration
  - Vomiting
  - Diarrhea
  - Polyuria
- Interstitial fluid redistribution:
  - Thermal injury
  - Trauma
  - Anaphylaxis
- Increased vascular capacitance:
  - Sepsis
  - Anaphylaxis
  - Toxins/drugs

Cardiogenic

- Myopathy:
  - Myocardial infarction:
    - Left or right ventricle
  - Myocardial contusion
  - Myocarditis
  - Cardiomyopathy
  - Post ischemic stunning
  - Septic myocardial depression
  - Pharmacologic:
    - Anthracycline cardiotoxicity
    - Calcium channel blockers
- Mechanical:
  - Valvular failure (stenotic or regurgitant)
  - Hypertrophic cardiomyopathy
  - Ventricular septal defect
- Arrhythmic:
  - Bradycardia
  - AV blocks
  - Tachycardia:
    - Supraventricular
    - Ventricular

Obstructive

- Impaired diastolic filling (decreased preload):
  - Vena cava obstruction

- Intrathoracic obstructive tumors
- ↑ intrathoracic pressure
- Tension pneumothorax
- Mechanical ventilation
- Decreased cardiac compliance
- Constrictive pericarditis
- Cardiac tamponade:
  - Acute:
    - Post-MI free wall rupture
    - Traumatic
    - Hemorrhagic
  - Chronic:
    - Malignant
    - Uremic
    - Idiopathic

- Impaired systolic contraction:
  - Right ventricle:
    - Pulmonary embolus
    - Acute pulmonary hypertension
  - Left ventricle:
    - Saddle embolus

Aortic dissection

Distributive

- Septic
- Toxic shock syndrome
- Anaphylactic
- Neurogenic (spinal shock)
- Endocrine:
  - Adrenal crisis
  - Thyroid storm
- Toxins

Typical presentation

- Typically, in adults, the systolic blood pressure is less than 90 mmHg and the mean arterial pressure is less than 70 mmHg. This is associated with tachycardia.
- This tissue hypoperfusion can be identified early by paying attention to what is referred to as the 'three windows' of the body:
  - Cutaneous: skin becomes cold and clammy due to vasoconstriction or due to severely inadequate cardiac output with vasodilation.
  - Kidneys: urine output of <0.5 mL/kg/h.
  - Neurologic: altered sensorium (obtundation, disorientation, and/or confusion).
- Hyperlactatemia (>1.5 mmol/L) is typically present.

Clinical diagnosis

History

- The state of circulatory shock is always a life-threatening condition and is an emergency. It is imperative that the diagnosis is made as early as possible, preferably at the compensated stage.
- In the compensated state hypotension may not be apparent, therefore reliance on the presence of hypotension is not recommended. Additionally, mortality is already increased if hypotension and hypoperfusion are present.
- Because survival is dependent on early initiation of therapy for shock, diagnosis of shock is always a clinical diagnosis. Laboratory tests and imaging can be performed to support the diagnosis or to identify the underlying etiology; however, therapy should not be delayed to accommodate laboratory studies.
- Just as circulatory shock is a common end pathway for a variety of etiologies, treatment of all forms of shock mainly follows a common pathway.

Physical examination

- Physical exam is extremely important in recognizing shock and can be grouped into two main areas. The first is recognizing the physical signs of compensatory mechanisms that come into play during the initial phase (pre-shock) of shock.
- Examination is accomplished by paying attention to the physical manifestations in the 'three windows' of the body (cutaneous, neurological, renal). Early signs that reflect the body's effort to compensate include tachycardia, dyspnea, and oliguria (urine output <0.5 mL/kg/h). Additionally, the extremities are cool and may get mottled.

- Blood pressure may be elevated or even normal initially when the patient is in a compensated state with maximal sympathetic drive. Clinicians should consider the baseline blood pressure of the patient. Normotension in a patient who is otherwise hypertensive may indicate hypoperfusion. Frank hypotension (MAP <60–65 mmHg) will develop if untreated as the shock state progresses.
- Other clinical signs may be sought to identify the type and etiology of the shock:
  - Hypovolemic shock – look for decreased JVP.
  - Cardiogenic shock – look for elevated JVP and presence of S3 and S4 with or without murmurs.
  - Obstructive shock:
    - Pulmonary embolus – look for signs of RV failure, dyspnea, and hypoxia.
    - Cardiac tamponade – look for Kussmaul's sign, distant heart sounds, and pulsus paradoxus.
  - Septic shock – look for fever, abnormal WBC, warm extremities, and focus of infection.

Disease severity classification

Circulatory failure resulting in shock and its progression to death, irrespective of etiology, does not show abrupt changes and is rather a pathophysiologic continuum. However, three stages can be identified.

Stage	Explanation of stage
Pre-shock	A stage in the shock continuum where compensatory mechanisms become active and an attempt to restore tissue perfusion is maintained. During this phase, mild tachycardia, mild to moderate reduction in blood pressure, and mild elevation of lactate levels may be the only manifestation in a patient with appropriate setting for development of shock
Shock	A stage where the compensatory mechanisms become overwhelmed by the underlying disease progression with or without therapy. Clinical parameters for the diagnosis of shock such as severe tachycardia, hypotension, progressive severe lactic acidosis, oliguria, altered mental status, and other evidence of tissue underperfusion become apparent
End-organ dysfunction	Irreversible damage to multiple organs results in multiorgan failure. Resistant to therapy with worsening hypotension, severe reduction in cardiac output, acute renal failure, obtundation or coma, and finally death may ensue in this phase

Laboratory diagnosis

List of diagnostic tests

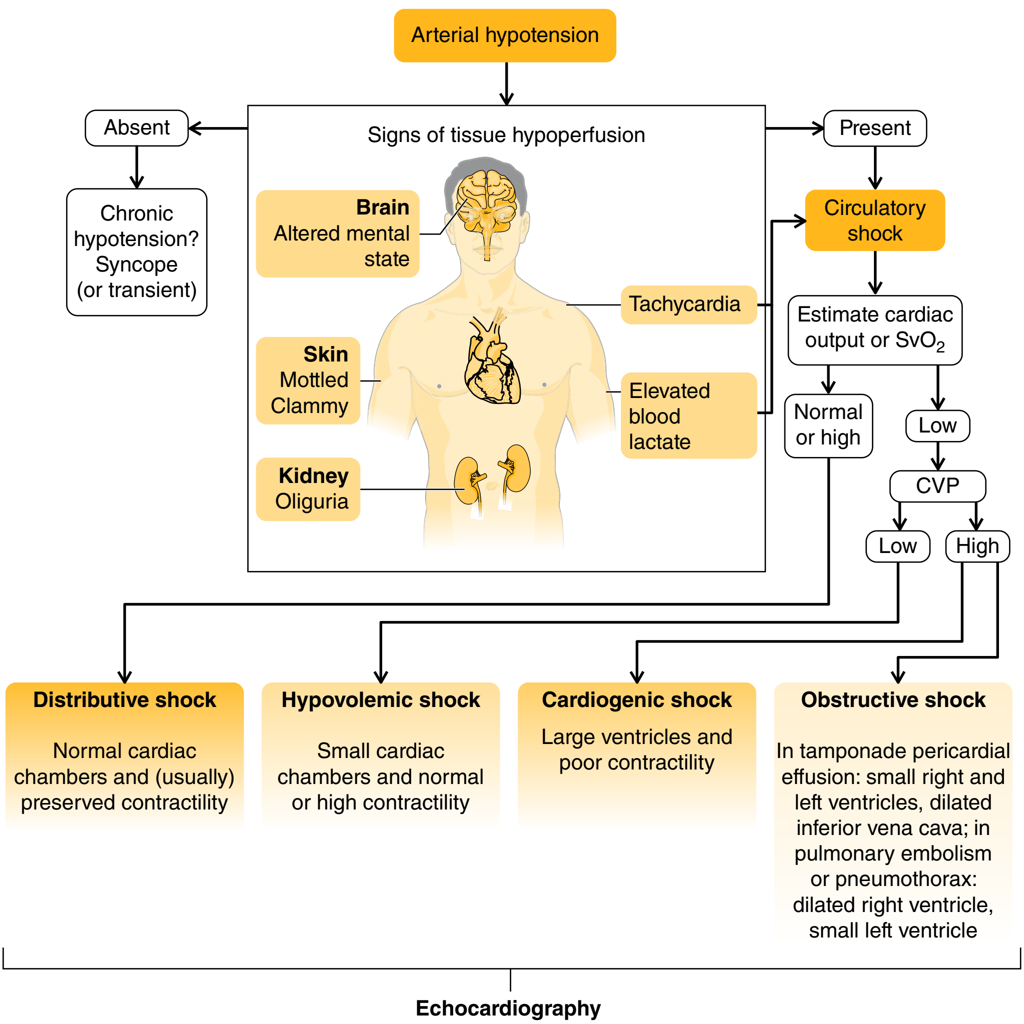
- Hemoglobin level: check to assess hemorrhage and oxygen-carrying capacity. Erythrocytosis may be evident in non-hemorrhagic hypovolemic shock and in septic shock when extravasation of intravascular fluid into the interstitium.
- WBC: leucocyte count is usually elevated despite the etiology of shock due to demargination of neutrophils but leucopenia can manifest in the case of late shock or sepsis.
- Platelets: platelet count increases acutely due to stress of shock but thrombocytopenia can result with progression of sepsis or with massive resuscitation efforts to correct hemorrhage.
- Arterial blood gases and electrolytes:
  - An anion gap acidosis usually associated with lactic acidosis indicates prolonged periods of tissue underperfusion.
  - Non-anion gap acidosis in hypovolemia may indicate excessive diarrhea.
  - In hypovolemic shock, metabolic alkalosis may indicate vomiting.
- BUN/creatinine: these may be initially normal even if there is underlying renal injury. Isolated increase in BUN without increase in creatinine may suggest GI bleed.
- Coagulation studies: performed if coagulopathy as a result of shock is suspected.
- ECG: helps detect myocardial ischemia and if pathologic tachycardia is suspected.

List of imaging techniques

- Chest radiograph: to identify pneumonia, pulmonary edema, pneumothorax, and significant pericardial effusion.
- The following are optional:
  - Abdominal radiograph is rarely needed unless intra-abdominal obstructive processes are suspected.
  - CT scan of the chest and abdomen are useful in specific situations such as aortic dissection, intra-abdominal hemorrhage, and pulmonary embolus.
  - Echocardiogram is useful for the diagnosis of multiple etiologies of shock such as pulmonary embolus, LV or RV failure, pericardial tamponade, and other repairable cardiac lesions such as acute mitral regurgitation or aortic regurgitation.
  - MRI (if the patient is able to tolerate it) is useful for the diagnosis of acute myocarditis and the presence of infiltrative cardiomyopathies resulting in restrictive filling and low cardiac output. It is also useful for accurate RV function assessment.

Diagnostic algorithm (Algorithm 18.1)

Algorithm 18.1 Initial assessment of shock. (Source: Reproduced with permission from Vincent et al. 2013.)



Potential pitfalls/common errors made regarding diagnosis of disease

- Awaiting development of hypotension to identify development of hypotension is a common error and results in delay in useful interventions or searching for underlying etiologies in a timely manner.
- Beware of the patient's baseline systolic pressure. In a hypertensive patient, drop in pressure by 40 mmHg from baseline can signal development of shock state even if the MAP (<60–65 mmHg) does not meet the criteria for hypotension.
- Once shock state is clinically identified, awaiting laboratory confirmation to start appropriate therapy is another common error encountered in the critical care setting.

Treatment

Treatment rationale

- Treatment rationale of shock consists of efforts to maintain adequate perfusion to match oxygen delivery and oxygen consumption in addition to correcting the underlying etiology of the shock.
- Initial approach is fluid resuscitation along with adequate oxygenation.
- Vasoactive substances are then administered to maintain adequate perfusion.
- Failure of vasoactive medications should lead to consideration for early institution of cardiac assist device support. Restoration of adequate cardiac output will not result in improvement once microcirculatory failure ensues.
- If all aggressive measures fail and continuation becomes futile, palliation and comfort care are considered.
- There are four phases of treatment: salvage, optimization, stabilization, and de-escalation.

Managing the hospitalized patient

Stage	Four phases of treatment
Pre-shock	*Salvage* Focuses on achieving adequate blood pressure and cardiac output and immediately correcting the underlying cause of shock: • Attempt at maintaining acceptable blood pressure (MAP >60–65 mmHg) is initiated • Life-saving interventions are promptly initiated. For example: acute coronary revascularization or assist devices for cardiogenic shock from acute MI; prompt antibiotic coverage for septic shock; acute thrombolysis or thrombectomy in the case of massive PE; pericardiocentesis for tamponade, etc.
Shock	*Optimization* Focuses on factors that improve cellular oxygen delivery and availability: • Maintain adequate tissue oxygen availability by optimizing CO, SvO_2 and lactate levels *Stabilization* Focuses on preventing organ dysfunction even if hemodynamic stabilization has been established. Establishing hemodynamic stabilization in shock syndrome does not guarantee end-organ function improvement: • Provide organ support and attempt to minimize complications *De-escalation* Focuses on weaning from vasoactive agents as the condition of the patient improves: • Wean from vasoactive agents and achieve negative fluid balance
End-organ dysfunction	If SIRS and subsequent multiorgan failure/MODS develops, the risk of death increases substantially (>75%). Aggressive treatment may become futile and can perpetuate patient and family suffering. At this stage it is appropriate to involve the service of palliative care medicine and initiate goals of care conversation with patient/family

Table of treatment

Treatment	Comments
Conservative Fluid resuscitation Oxygen delivery (nasal cannula, high flow nasal cannula, or ventilator)	Fluid administration is a conservative initial measure to improve cardiac output and microvascular flow. Oxygen is administered to improve the oxygen content
Medical Norepinephrine (0.1–2.0 μg/kg/min) Dopamine (2–20 μg/kg/min) Epinephrine (0.05–2 μg/kg/min and titrated up) Vasopressin (0.03 U/min and titrated up) Dobutamine (2–20 μg/kg/min) Milrinone (0.125–0.75 μg/kg/min)	Once shock state is recognized, vasopressor support is recommended to maintain arterial perfusion pressure while inotropic support may be needed to enhance cardiac output of failing ventricles. All patients should be considered for resuscitation with vasoactive medications unless specific contraindication exist (e.g. arrhythmia prohibiting the use of pro-arrhythmic drugs such as dobutamine or dopamine)
Surgical Various right and left ventricular devices, usually emergent/short-term devices Pericardiocentesis Pulmonary thrombectomy	Patients who decline despite maximal medical therapy should be considered for early percutaneous short-term or long-term cardiac device support to ensure adequate oxygen delivery. The choice of device depends on the resources and the experience of the institution. Surgical pulmonary thrombectomy can be considered for acute PE resulting in obstructive shock
Radiologic Pulmonary thrombectomy	Considered in acute massive PE
Psychologic Spiritual care Palliative care	All patients and family should receive these interventions when appropriate

Prevention/management of complications

- Critically ill shock patients frequently have multiple invasive catheters placed for monitoring and treatment purposes.
- One of the most feared complications is the development of line-related sepsis in addition to an existing shock from other etiology such as cardiogenic or hypovolemic shock. This can be prevented by vigiliant monitoring and removing indwelling catheters when not necessary and by limiting the use of indwelling catheters in general.
- Development of ventilator-associated pneumonia is another potential complication in patients with prolonged ventilator dependence. Application of prophylactic measures and daily assessment for the liberation from ventilator support should be instituted to prevent this complication.
- Persistent hypotension despite aggressive efforts should raise concern for adrenal suppression/insufficiency. This can be managed by administering corticosteroids.
- With the use of multiple vasoactive medications, development of arrhythmia is a common complication that may result in clinical decompensation. Clinicians should consider cardioversion or rhythm control versus rate control strategies carefully. It is important to carefully select vasoactive medications keeping the patient’s underlying risk factors in mind.

CLINICAL PEARLS

- Shock syndrome is a condition resulting from a mismatch between oxygen delivery (DO_2) and consumption (VO_2). Both oxygen delivery and consumption should be considered when tailoring interventions.
- Microcirculatory failure of individual organs and specific vascular beds may continue to drive the downward spiral despite achievement of adequate cardiac output. As a result, continued vigilance and aggressive clinical support is required despite achieving hemodynamic stability.
- Gut wall integrity as well as perfusion should be optimized to avoid development of septicemia from translocation of microbes from the gut due to the loss of gut integrity.

Special populations

Pregnancy

- Pregnant women tend to suffer hypovolemic shock from obstetrical hemorrhage.
- Pulmonary embolism (PE) and venous thrombosis are known to occur in the peripartum period. In fact, PE is the sixth leading cause of maternal mortality.
- Septic shock is not frequent in pregnant women; however, most studies on sepsis have excluded pregnant women.
- From a cardiac perspective, peri-partum cardiomyopathy may result in cardiogenic shock at the time of delivery due to sudden increase in afterload and could be fatal.
- Principles of treatment are generally extrapolated from the general adult population and applied to the pregnant population.
- Management of circulatory failure in pregnant women should involve a multidisciplinary team approach involving maternal–fetal medicine, neonatology, and intensivists as well as cardiac anesthesia if a cesarean is considered.

Elderly

- Management of shock syndromes in the elderly is very similar to that in other adult patients. However, more clinical vigilance is recommended as elderly patients are less tolerant of the mismatch of oxygen delivery and consumption resulting from circulatory shock, and may suffer a rapid decline.
- In very elderly patients, early involvement of geriatric medicine and palliative care medicine may be beneficial.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Circulatory shock from any cause results in very high mortality despite advances in therapy.
- By the time severe shock syndrome and its complications develop, the initial etiology of shock may have little impact in the prognosis due to the confluence of multiple shock hemodynamics.
- Reversal of the downward spiral in circulatory shock may become irreversible if shock is not detected and managed at an early stage.

Natural history of untreated disease

- Since circulatory shock is a syndrome that reflects failure of multiple organ systems, the condition will continue to worsen without early and appropriate interventions.
- The survival of patients with untreated shock remains dismal.

Prognosis for treated patients

- Mortality in cardiogenic shock even when treated remains at an unacceptable rate of more than 40%.
- Fatality of septic shock is estimated at 40–50%, reaching as high as 80%.
- Hypovolemic shock can be successfully treated and survival rates are higher than for septic and cardiogenic shock. The exception is hypovolemic shock in trauma patients where the mortality is determined by the severity of trauma that resulted in hypovolemia.
- Mortality of obstructive shock is determined by the underlying etiology.

Follow-up tests and monitoring

- Early treatment includes hemodynamic stabilization with fluids and vasopressors and treatment of the underlying etiology. Frequent reassessments are essential.
- It is reasonable to use hemodynamic assessment (pulmonary artery catheterization) in complex patients who do not respond to initial efforts.
- Insertion of arterial and central venous catheters is also recommended when there is inadequate response to initial therapy or need for continuous infusion of vasopressors.
- If a central venous catheter is present, measurement of $ScvO_2$ to monitor the underlying pattern and adequacy of cardiac output to guide therapy is recommended.
- Serial lactate levels have been shown to be useful to assess response to therapy.

Reading list

Cecconi M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task Force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;40:1795–815.

Kumar A, Unligil U, Parrillo JE. Circulatory shock. In: Unligil U, Parrillo JE (eds), Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 4th edition. Philadelphia: Elsevier, 2013; pp. 299–324.

Lim HS. Cardiogenic shock: failure of oxygen delivery and oxygen utilization. Clin Cardiol 2016;39(8):477–83.

Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. Nat Rev Cardiol 2016;13(8):481–92.

Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369:1726–34.

Suggested websites

http://www.esicm.org

Guidelines

International society guidelines

Title	Source	Date and weblink
Consensus on Circulatory Shock and Hemodynamic Monitoring	European Society of Intensive Care Medicine	2014 http://www.esicm.org

Image

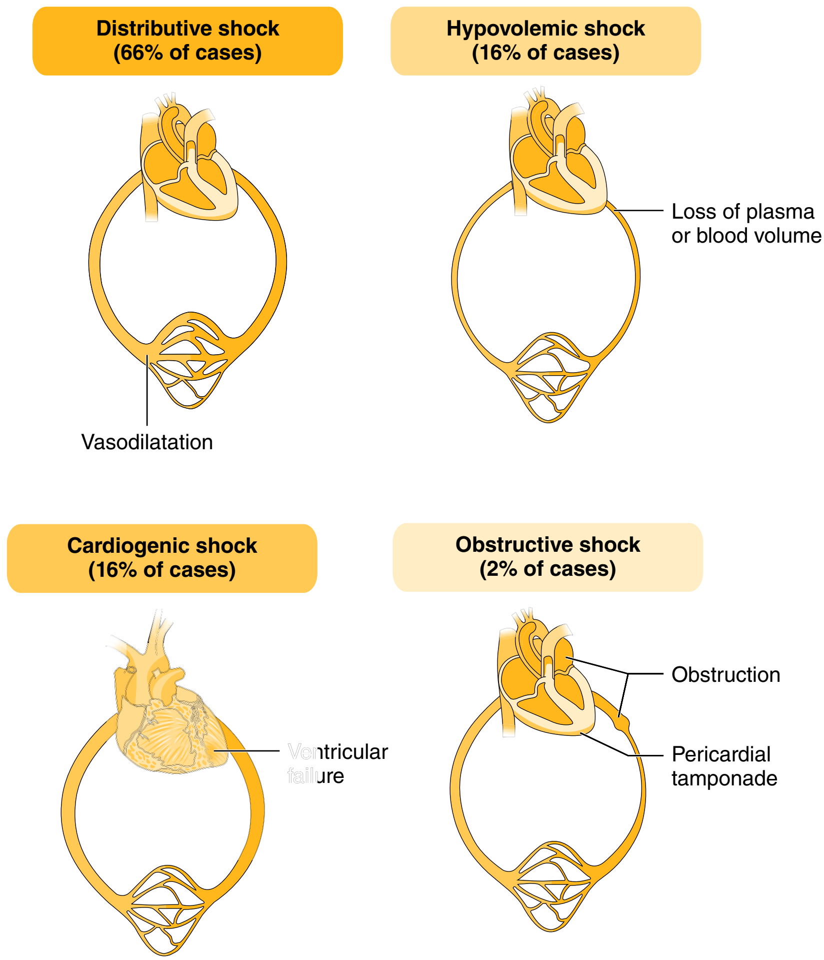


Figure 18.1 Frequency of the four main four types of shock

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 19

Cardiac Arrest

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OVERALL BOTTOM LINE

- Untrained lay rescuers should provide compression-only (hands-only) CPR for adult victims of cardiac arrest.
- Defibrillation should be performed as soon as possible, either immediately or after 2 minutes of CPR, if the initial rhythm is ventricular fibrillation or tachycardia.
- Amiodarone or lidocaine are indicated in cardioversion-resistant ventricular fibrillation.
- Therapeutic temperature modulation to a target temperature of 33–36°C for 24 hours is recommended in patients resuscitated from a shockable rhythm, and suggested in patients with a non-shockable rhythm.
- Testing to determine neurologic prognosis should be performed no sooner than day 3, and a longer observation period is strongly recommended.

Background

Definition of disease

- Cardiac arrest is the cessation of cardiac activity resulting in the abolition of circulation.

Disease classification

- Cardiac arrest is traditionally categorized as being of cardiac or non-cardiac origin (e.g. driven by respiratory failure, sepsis, or trauma).
- The type of arrest is defined by the initial cardiac rhythm:
  - Ventricular fibrillation (VF) or ventricular tachycardia (VT), the two shockable rhythms: 20%.
  - Pulseless electrical activity (PEA): 35%.
  - Asystole: 45%.

Incidence/prevalence

- Each year 326 000 people experience EMS-assessed out-of-hospital cardiac arrests in the USA.
- Approximately 50% of out-of-hospital cardiac arrests are witnessed, and 60% are treated by EMS providers.
- In 2013 survival to discharge was 10% overall, but 33% for patients with witnessed VF or VT.
- About half of cardiac arrest survivors regain consciousness and have a good neurologic outcome.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Etiology

- Coronary artery disease resulting in acute myocardial infarction or ischemic cardiomyopathy is the most common cause of sudden cardiac arrest.
- Primary cardiac conduction abnormalities.
- Non-ischemic cardiomyopathy.
- Drug intoxication, including opioid overdose.
- End-stage renal failure patients on dialysis.

Prevention

> **BOTTOM LINE/CLINICAL PEARLS**
>
> - In general, treatment of hypertension, diabetes, and heart disease are the best methods of reducing the incidence of sudden cardiac arrest.

Diagnosis

- Patients with sudden cardiac arrest present with sudden collapse and loss of consciousness.
- In an unmonitored setting, the key to diagnosis is to establish *unresponsiveness* to verbal and tactile stimuli, *apnea*, and *pulselessness*.
- In a monitored setting, or as soon as a cardiac monitor can be placed, the diagnosis can be established by demonstrating VF, VT, or asystole.
- PEA is established when cardiac monitoring shows organized electrical activity but the patient is pulseless and unresponsive.

Basic cardiac life support

The 2019 AHA guidelines for performing high quality CPR for out- of- hospital cardiac arrest patients without an advanced airway is shown in the box.

> **Considerations in Performing High-Quality CPR**
>
> - Perform chest compressions at a rate of 100–120/min
> - Compress to a depth of at least 2 inches (5 cm)
> - Allow for full recoil after each compression
> - Minimize pauses in compressions (no more than 10 seconds for a pulse check)
> - Ventilate adequately (2 breaths after 30 compressions, each delivered over 1 second, each causing chest rise)

Chest compressions

- Untrained lay rescuers should provide compression-only (hands-only) CPR for adult victims of cardiac arrest.
- In addition, if a trained rescuer is able to perform rescue breaths, he or she should add rescue breaths in a ratio of 30 compressions to 2 breaths.
- The rescuer should continue CPR until an AED arrives and is ready for use, EMS providers take over care of the victim, or the victim starts to move.
- The 2015 AHA guidelines suggest against the routine use of automated mechanical chest compression devices to replace manual chest compressions

Chest compression rate

- In most studies, longer durations of chest compressions are associated with higher survival rates, and fewer compressions are associated with lower survival rates.
- The 2019 AHA guidelines recommend a manual chest compression rate of 100–120 bpm.

Chest compression depth

- During manual CPR, rescuers should perform chest compressions to a depth of at least 5 cm (2 inches) for an average adult, while avoiding excessive chest compression depths (greater than 6 cm (2.4 inches)).
- Rescuers should avoid leaning on the chest between compressions to allow full chest wall recoil for adults in cardiac arrest.

Compression : ventilation ratio

- The 2015 AHA guidelines suggest a compression : ventilation ratio of 30:2 in patients in cardiac arrest.
- If an advanced airway is in place (e.g. if the patient has arrested while on mechanical ventilation or if a bag-valve-mask is applied) it may be reasonable for the provider to deliver 1 breath every 6 seconds (10 breaths per minute) while continuous chest compressions are being performed.

Bystander naloxone in opioid-associated life-threatening emergencies

- For patients with known or suspected opioid addiction who are unresponsive with no normal breathing but a pulse, it is reasonable for appropriately trained lay rescuers and BLS providers to administer intramuscular or intranasal naloxone in addition to providing standard BLS care.

Shock first versus CPR first

- For witnessed adult cardiac arrest when an AED is immediately available, it is reasonable that the defibrillator be used as soon as possible.
- For adults with unmonitored cardiac arrest or for whom an AED is not immediately available, it is reasonable that CPR be initiated while the defibrillator equipment is being retrieved and applied and that defibrillation, if indicated, be attempted as soon as the device is ready for use.

Advanced cardiac life support

Epinephrine

- The 2019 AHA guidelines suggest that for cardiac arrest with an initial non-shockable rhythm, epinephrine should be given as soon as possible.
- These guidelines suggest vasopressin should not be used instead of epinephrine in cardiac arrest.
- These guidelines suggest considering use of vasopressin in combination with epinephrine, but note that this does not confer an advantage compared to alone.
- These guidelines suggest against the routine use of high-dose epinephrine (5 mg) as opposed to standard-dose epinephrine (1 mg), in cardiac arrest.

Use of Advanced Airways

- The 2019 AHA guidelines suggest that either bag mask ventilation or an advanced airway strategy (supraglottic airway device or endotracheal intubation) may be considered during CPR.
- When delivering ventilation, chest compressions should not be interrupted. Verntilation should be provided during chest compressions at a rate of 10 breaths per minute.

Antiarrhythmic drugs

- The 2015 AHA guidelines suggest the use of amiodarone 150 mg in repeated doses in adult patients with refractory VF/VT to improve rates of return of spontaneous circulation (ROSC).
- These guidelines also suggest the use of lidocaine or nifekalant (for both give 1 mg/kg, repeat twice for a maximum dose of 3 mg/kg) as an alternative to amiodarone in adult patients with refractory VF/VT.
- These guidelines recommend against the routine use of magnesium in adult patients.

Table 19.1 PEA evaluation.

QRS narrow	QRS wide
Mechanical (RV) problem:	Metabolic (LV) problem:
Cardiac tamponade	Severe hyperkalemia
Tension PTX	Sodium channel blocker toxicity
Mechanical hyperinflation	Agonal rhythm
Pulmonary embolism	
Acute MI: myocardial rupture	Acute MI: pump failure
Bedside US: LV hyperdynamic, pseudo-PEA	Bedside US: LV hypokinetic or akinetic, true PEA

Differential diagnosis of PEA arrest

- PEA is when the cardiac monitor shows organized electrical activity but the patient is pulseless and unresponsive.
- There are 12 treatable or reversible causes of PEA arrest. Seven start with the letter H, and 5 start with the letter T:
  - '7 Hs': hypovolemia, hypoxia, hydrogen ion excess (acidosis), hypoglycemia, hypokalemia, hyperkalemia, hypothermia.
  - '5 Ts': tension pneumothorax, tamponade, toxins, thrombosis (pulmonary embolism), thrombosis (myocardial infarction).
- The cause of PEA can be further classified as metabolic or obstructive based on the presence of narrow or wide QRS complexes (Table 19.1).

Resuscitative transesophageal echocardiography (TEE)

- Resuscitative TEE is an emerging advanced technique for imaging the heart during or immediately after CPR. Its main advantage is that imaging the heart via the esophagus does not interfere with chest compressions.
- TEE can diagnose two syndromes during cardiac arrest that can influence management:
  - Pseudo-PEA: pulseless due to profound shock with preserved LV contractility. Treatment is to give inotropes and high dose vasopressors.
  - Fine VF: cardiac monitor appears to show asystole but heart is shown to be fibrillating. Treatment is repeated attempts at cardioversion.

Cardiocerebral resuscitation

Diagnosis and management of acute coronary syndromes

BOTTOM LINE

- A substantial proportion of cardiac arrest patients are also suffering from an acute coronary syndrome (ACS) (myocardial infarction). This is especially true for patients who present with VF or VT.
- For this reason it is important to screen for ACS in all patients presenting with cardiac arrest once they have been stabilized.
- Testing should include at a minimum:
  - 12-lead ECG.
  - Cardiac enzymes (troponin I).
  - B-type natriuretic peptide.
  - Arterial lactate and ABG.
  - Neuron-specific enolase (daily for 3 days to evaluate neurologic prognosis).
  - CBC, basic metabolic panel, magnesium, PT, and PTT.

- Triage of candidates for percutaneous coronary intervention (PCI):
  - If the initial rhythm was VF or VT with ROSC of ≤30 minutes, the cardiac arrest team is activated, and the patient will proceed immediately to the cardiac catheterization laboratory.
  - If the initial reported arrhythmia was PEA or asystole, the next step will depend on the ECG performed in the ED. If the ECG performed in the ED is suggestive of priority ACS (including ST elevation MI, left bundle branch block, or acute posterior wall MI), the MI team should be activated, and the care is similar to those patients with VF/VT arrest.
  - If priority ECG findings are not seen but the etiology of the arrest is most likely due to primary cardiac disease (i.e. valvular heart disease or non-ischemic cardiomyopathy), admit the patient to the cardiac care unit and obtain an emergency echocardiogram.
  - If the etiology is likely non-cardiac the patient will be admitted to the medical intensive care unit.

Therapeutic temperature modulation

BOTTOM LINE

- Therapeutic temperature modulation (TTM) to 33°C, also known as hypothermia, has been shown in randomized trials to improve survival and neurologic outcome in VF/VT and in patients with non-shockable rhythms patients who had obtained ROSC after cardiac arrest.
- The more recent TTM trial (2014) showed similar good outcomes in VT/VF patients treated to a target of either 33°C or 36°C.
- In response to these data, the International Liaison Committee on Resuscitation (ILCOR) *recommends* TTM to a target of 33–36°C for 24 hours for comatose adult VT/VF patients who have attained ROSC after cardiac arrest.
- The strength of the evidence for in-hospital cardiac arrest is not as strone. For this reason ILCOR *suggests* TTM as a therapeutic option in these scenarios.

Who to treat with TTM?

- The decision to initiate induced hypothermia is usually made jointly by the ED physician and the cardiology or critical care physician.
- Patients must be comatose, not following commands or demonstrating purposeful movements, indicating a major brain injury.
- Head CT should be considered in patients suspected to possibly have suffered a subarachnoid hemorrhage as the cause of the arrest.
- Suggested criteria for inclusion and exclusion criteria are shown in Table 19.2. Note that in this algorithm both shockable and non-shockable rhythms are considered appropriate for TTM.

Induced therapeutic hypothermia protocol

- The hypothermia protocol is divided into three phases:
  - Phase 1: cooling phase for the first 24 hours.
  - Phase 2: rewarming phase.
  - Phase 3: maintenance phase.

Table 19.2 Inclusion and exclusion criteria for TTM therapy after cardiac arrest.

Inclusion:
- Age >18 years
- Coma at the time of cooling (not following commands)

Exclusion:
- Patient awake and follows commands
- Known terminal illness or DNR
- Refractory shock despite vasopressors
- Pregnancy (relative contraindication)
- Multi-system organ failure

Phase 1: cooling phase for the first 24 hours

- We recommend 24 hours of the cooling therapy.
- A target temperature goal of 33–36°C is most appropriate. Note that there is a higher risk of cardiac complications with lower temperatures.
- Continuous core temperature monitoring is required and can be accomplished using a temperature probe in the bladder, esophagus, or rectum.
- Advanced cooling devices adjust the water temperature to maintain core temperature within a tight range.
  - Endovascular heat exchange catheters (e.g. Zoll Cool Line) are usually inserted into the inferior vena cava through the femoral vein.
  - Adhesive surface cooling systems (e.g. Bard Arctic Sun) are applied to the thorax and anterior thighs.
- Complications and side effects of hypothermia:
  - *Cardiac depression*: bradycardia and reduced LV contractility.
  - *Coagulopathy*: PT and PTT prolongation.
  - *Immunosuppression*: increased risk of hospital-acquired infections (pneumonia most common).
  - *Metabolic derangements*: hypokalemia, hyperglycemia.
- *Shivering*: fights the cooling process and increases systemic and cerebral energy expenditure and oxygen consumption. Use the bedside shivering assessment scale (BSAS) to measure shivering, and the Columbia anti-shivering protocol to control it to a target BSAS score of 0 or 1 (scale 0–3).

COLUMBIA ANTI-SHIVERING PROTOCOL

- Standing orders:
  - Acetaminophen 650 mg every 4 hours
  - Buspirone 30 mg PO every 8 hours
- PRN shivering 1:
  - Mg^{2+} infusion 1–2 g/h (target level 3–4 mg/dL)
  - Skin counterwarming
- PRN shivering 2:
  - Dexmedetomidine 0.3–1.5 µg/kg/h
- PRN shivering 3: select one of the following
  - Meperidine 25–100 mg IV
  - Fentanyl 50–200 µg/h
  - Propofol 25–100 µg/kg/min

BEDSIDE SHIVERING ASSESSMENT SCALE

- Palpate the masseters, pectoralis, biceps, and quadriceps muscles.

Score	Findings
0	No shivering
1	Palpable shivering localized to the head, neck, and chest
2	Visible shivering of the arms
3	Visible shivering of all four extremities

Phase 2: rewarming phase

- After 24 hours at target temperature, the rewarming phase starts.
- Rewarming should be slow; we recommend a rate of 0.25°C per hour; therefore it typically requires 16 hours to rewarm from 33°C to 37°C.
- Potential complications during the rewarming phase include:
  - Hypotension, owing to peripheral vasodilation.
  - Hyperkalemia and other electrolyte imbalances.

Phase 3: maintenance of normothermia phase

- Normothermia (37°C) should be strictly maintained for at least 48 hours after rewarming to prevent rebound fever.

Special populations

Pregnancy

- In general it is recommended to treat the mother as the sole priority. Survival of the fetus depends on successful resuscitation of the mother.

Children

- Refer to separate AHA BLS, ACLS, and post-resuscitation care guidelines for children who suffer cardiac arrest (professional.heart.org).

Prognosis

- On day 3, after rewarming is completed, assessments can be performed to evaluate the neurologic prognosis if the patient remains comatose.
- There are five components of multimodality assessment of neurologic prognosis after cardiac arrest:
  - Neurologic examination off sedation:
    - Absent pupillary and motor responses imply poor prognosis.
  - 48 hours of surveillance of continuous EEG:
    - Electrographic seizures occur in 20% of patients, require treatment, and imply poor prognosis.
  - Peak neuron-specific enolase level at 24–48 hours:
    - Levels exceeding 80 μg/dL imply poor prognosis.
  - Brain MRI: FLAIR, DWI, and ADC sequences:
    - DWI abnormalities involving ≥10% of brain volume imply poor prognosis.
  - Median nerve somatosensory potentials:
    - Absent bilateral N20 cortical potentials implies poor prognosis.

- If the prognosis appears unfavorable, we recommend activating the ethics committee to meet with the family and clinicians to define the goals of care.

Follow-up tests and monitoring

- If outcome is good and there is no evidence of acute MI (negative cardiac markers) then we recommend electrophysiology service consultation for consideration of implantable cardioverter defibrillator (ICD) placement.
- If acute MI is confirmed and LVEF is ≤35% we recommend consideration of ICD placement

Reading list

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Hazinski, MF, et al. Part 1: Executive summary. 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2015; 132(Suppl 1):S2–39.

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Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.

Nielsen N, et al; TTM Trial Investigators. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197–206.

Wong CX, et al. Epidemiology of sudden cardiac death: global and regional perspectives. Heart, Lung and Circulation. 2019;28:6–14.

Guidelines

International society guidelines

Title	Date and reference
2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations	2015 Hazinski MF, et al. Circulation 2015;132(Suppl 1):S2–39
2019 American Heart Association focused update on advanced cardiovascular life support: use of advanced airways, vasopressors, and extracorporeal cardiopulmonary resuscitation during cardiac arrest: an update	2019 Panchal AR, et al. Circulation 2019;140(24):e881–94

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

with website

PART 3

Pulmonary Critical Care

Section Editor: Hassan Khouli

CHAPTER 20

Respiratory Monitoring

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OVERALL BOTTOM LINE
- Respiratory monitoring involves physical examination, device use, and diagnostic testing with the goals of recognizing and managing respiratory failure.
- In critically ill patients, the major respiratory parameters that should be routinely monitored are respiratory rate, tidal volume, and oxygenation.
- Monitoring of end expiratory carbon dioxide and serum pH are desirable in certain circumstances.

Importance of respiratory monitoring

- Respiratory monitoring is required for the management of patients at high risk of respiratory failure or established respiratory failure.
- Monitoring processes are methods to identify respiratory failure. These range from physical examination to non-invasive and invasive techniques.
- Patients on mechanical ventilation require continuous monitoring to assure adequate oxygenation and ventilation, as well as correct placement of the life support devices.

Major types of respiratory monitoring

- Bedside examination.
- Impedance monitors.
- Pulse oximetry.
- Capnography.
- Arterial blood gas analysis.
- Ventilator waveform.
- Muscle strength.
- Imaging.

Definition of respiratory failure

Type I: hypoxemic respiratory failure

- PaO_2 <60 mmHg breathing room air at sea level.
- Mechanisms include (usually in combination):
  - Ventilation/perfusion mismatch.
  - Shunt.
  - Hypoventilation/respiratory muscle insufficiency.
  - Diffusion impairment.
  - A low mixed venous PO_2 from low cardiac output will augment the effect of shunt.
- Hypoxemia in ARDS can be classified by the PaO_2/FiO_2 ratio into mild (PaO_2/FiO_2 ≤300 mmHg but >200 mmHg), moderate (PaO_2/FiO_2 ≤200 mmHg but >100 mmHg), and severe (PaO_2/FiO_2 ≤100 mmHg).

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Type 2: hypercapneic respiratory failure

- $PaCO_2$ >45 mmHg.
- Occurs with decreased alveolar minute ventilation.
- Mechanisms include:
  - Centrally mediated – respiratory depression.
  - Respiratory muscle failure.
  - Haldane effect.
  - V/Q mismatch.

Physical examination

Bedside examination

- Vital signs.
- Visual inspection:
  - Respiratory rate, pattern, depth, effort of breathing.
  - Inability to speak in full sentences.
  - Diaphoresis.
  - Use of accessory muscles.
- Mental status:
  - Alertness, restlessness, confusion, somnolence.
  - Asterixis (hypercapneic).
- Cyanosis*:*
  - With a normal Hb, central cyanosis corresponds to SpO_2 <50%.
- Lung examination:
  - Symmetry.
  - Lower airways: wheezes, rales, rhonchi.
  - Upper airway: stridor.
  - Distant or absent breath sounds: unilateral, percussion, tympanitic – pneumothorax, dullness – atelectasis or effusion.
- Thoraco-abdominal paradox (thorax ‘out’, abdomen ‘in’): respiratory muscle failure.

Patterns of breathing

- **Kussmaul respiration:**
  - Regular, increased frequency, increased tidal volume.
  - Can often be seen to be gasping.
  - *Indicates severe metabolic acidosis.*
- **Cheyne Stokes respiration:**
  - Respiratory alternans: cycling of high frequency and volume with low frequency and volume to apnea.
  - *May indicate brainstem injury, stroke, heart failure, or high altitude.*

Respiratory examination in neuromuscular disease

- Tongue weakness.
- Cough after swallowing – weak cough, aspiration.
- Hypophonia – wet, gurgling voice.
- Inability to raise the head due to neck muscle weakness.
- Difficulty in clearing secretions.
- Jaw weakness (jaw closure weaker than jaw opening).
- Orthopnea.
- Pausing during speech to take a breath.
- Staccato speech or a nasal quality to speech.
- Diaphragmatic dysfunction – inability to lie flat.

Impedance monitors

- Commonly used to measure respiratory rates and approximate tidal volume.
- Utilize ECG leads and measure changes in impedance generated by the change in distance between leads as a consequence of the thoraco-abdominal motions of breathing.
- Leads should be placed at points of maximal change in abdominal contour.
- Limitations:
  - Fail to detect obstructive apnea.
  - Detect tachypnea more accurately and may falsely report bradypnea.

Monitoring of oxygenation: pulse oximetry

- Routine for critically ill patients.
- Non-invasive, transcutaneous measurement of the oxygen saturation of hemoglobin in arterial blood by spectrophotometry and optical plethysmography.
- Oximeters distinguish between oxyhemoglobin and reduced hemoglobin on the basis of their different absorption of light (oxyhemoglobin absorbs less red and more infrared light than reduced hemoglobin).
- Probes are attached to digits, nose, ear lobes, or forehead (where the vascular density is much higher than other areas).
- The response time of the ear lobe measurement is faster than from the finger probes by approximately 6 seconds. Blood flow is measured from the supraorbital artery in which blood flow is abundant and less likely to be affected by vasoconstriction.

Benefits/accuracy

- Requires adequate perfusion.
- Closely correlates with direct arterial measurement in a well perfused patient when the oxygen saturation is in range of 70–100%.
- Essential method to monitor arterial oxygen saturation during transport of critically ill patients.

Potential pitfalls

- Unreliability:
  - Low flow states (Raynaud's, shock), irregular heart rates.
  - Severe anemia.
  - Motion artifact, hand tremors, Parkinson's disease.
  - Nail deformities, hyperpigmentation, nail polish.
- Caveats and technical difficulties:
  - Methemoglobin, carboxyhemoglobin, sulfhemoglobinemia: should assess with co-oximeter measurement on whole blood.
  - Hypothermia may cause poor quality signal (<35°C) or loss of signal detection (<26.5°C) due to vasoconstriction.
  - Normal values do not exclude tissue anoxia.
  - Normal values do not reflect adequate arterial oxygen content.
  - Strong electromagnetic waves affect the sensor readings. MRI safe system should be used. Severe burns associated with pulse oximetry have occurred in patients undergoing MRI.
  - Ambient light in the room may alter the photodetectors' sensitivity (e.g. in the operating room) and may cause falsely low or falsely high values depending on the light wavelengths (Table 20.1).
  - High venous pressures (e.g. compartment syndrome, tourniquet).

Table 20.1 Potential causes of false high and low values in pulse oximetry.

False low values	False high values
Compartment syndrome	Carboxyhemoglobin
Tourniquet or manometer cuff	Methemoglobin
Nail polish, acrylic nails, nail deformity	Severe anemia
Polycythemia	Elevated glycohemoglobin A1c (rarely)
Hyperpigmentation	Sulfhemoglobin
Methylene blue	

Using pulse oximetry in the ICU

- In a normal adult, the result of oxygen saturation obtained from an ABG must correlate with the SpO_2 obtained by the pulse oximetry probe. An oxygen saturation gap is present when there is more than a 5% difference.
- Pulse oximetry should not be used as a primary monitoring modality in the following situations:
  - During CPR.
  - In hypervolemia and shock.
  - For detecting worsening lung function in patients on a high concentration of oxygen.
  - For monitoring during induced or acquired hypothermia.

CLINICAL PEARLS

- Normal values on pulse oximetry do not exclude hypoxemia.
- When SpO_2 is below 70%, one cannot quantify the degree of oxygen saturation.
- For a patient with anemia, the SpO_2 may indicate adequate saturation of hemoglobin molecules, yet the total oxygen content will be low.
- In hypotensive patients, ear and forehead probes may be more reliable.
- In hypothermic patients, the forehead probe has been shown to be more reliable compared with the finger probe.
- In a patient with shivering, seizures, or Parkinson's tremor, the earlobe is the most reliable location for pulse oximetry.

Monitoring of ventilation: capnography

- Capnography is the measurement of exhaled CO_2 concentration over time.
- Capnography uses infrared absorbance to determine exhaled CO_2 values.
- Capnography monitors samples of expired CO_2 by using mainstream or sidestream techniques. The mainstream technique measures end-tidal carbon dioxide ($ETCO_2$) directly from the patient's respiratory circuit (sensor is located at the hub of the endotracheal tube) and is used in intubated patients. The sidestream technique measures $ETCO_2$ using a nasal cannula (sample gas is analyzed by a sensor inside the monitor) and is used in both non-intubated and intubated patients.
- Capnography reflects ventilation, perfusion, and metabolism and provides valuable information about the effectiveness of CO_2 elimination, CO_2 transport, and CO_2 production.
- Colorimetric capnography: filter color changes from purple to yellow and detects carbon dioxide and confirms tracheal intubation.
- Quantitative waveform capnography offers continuous, non-invasive measurement and graphic display of $ETCO_2$ (Figure 20.1).
- Qualitative capnography provides a range of $ETCO_2$ values (e.g. 0–10 mmHg or >35 mmHg).

Clinical uses

Acute clinical situation monitoring

- Confirmation of endotracheal tube placement.
- Qualitative assessment of cardiac output during CPR (ROSC).
- Qualitative assessment of airway obstruction in asthma (COPD).

Routine monitoring applications for capnography

- Monitoring of adequacy of ventilation and V/Q relationships.
- Monitoring mechanical ventilation: identification of leak or disconnection.
- Maintenance of endotracheal tube position (e.g. during transport).
- Monitoring sedation in a non-intubated patient (e.g. procedural sedation).
- Maintenance of optimal ventilation for hypocapnia in neurosurgery.

Capnograph waveform: four phases (Figure 20.1)

- *Phase I*: respiratory. Baseline: anatomic dead space → CO_2 = 0. Expiration begins.
- *Phase II*: expiration in progress. Mixture of alveolar gas with anatomic dead space:
  - Alpha angle: between phases II and III. Point of change from dead space airway gas to alveolar gas. Indirect indication of V/Q status of the lung.
  - Normally 110°. The larger airway obstruction, the larger the angle.
- *Phase III*: expiration. Elimination of CO_2 from the alveoli. Reaches a peak end-tidal partial pressure of CO_2 ($PETCO_2$). $PETCO_2$ in a normal individual is usually 2–3 mmHg lower than $PaCO_2$:
  - Beta angle: between phases III and IV. Maximal alveolar CO_2 concentration. Normal is 90°. Indirect measure of rebreathing.
- *Phase IV*: inspiration. Rapid decrease of CO_2 as CO_2-free gas is inhaled.

Causes of abnormal $ETCO_2$

Normal $ETCO_2$ 0–43 mmHg	**Increased $ETCO_2$ >43 mmHg**	**Decreased $ETCO_2$ <30 mmHg**
Ventilation	Hypoventilation (includes V/Q) Bronchoconstriction/asthma	Hyperventilation Intrapulmonary shunt Dislodged endotracheal tube
Circulation*	Successful CPR – ROSC Increased cardiac output Tourniquet release Treatment of acidosis	Apnea Cardiac arrest Pulmonary edema Pulmonary embolism Cardiogenic shock Hemorrhagic shock Intracardiac shunt
Metabolism	Fever/hyperthermia Malignant hyperthermia Seizure Burns Muscle use	DKA Sepsis Hypothermia Metabolic acidosis
Technical	Exhausted carbon dioxide absorber	Blocked endotracheal tube

*Increased cardiac output = increased $ETCO_2$. Decreased cardiac output = decreased $ETCO_2$

Interpretation of capnographs (Table 20.2)

Understanding the capnograph will allow recognition of potentially life-threatening situations in patients requiring mechanical ventilation as well as the effectiveness of CPR.

CLINICAL PEARLS

- Capnography provides valuable information about ventilation, perfusion, and metabolism.
- Under normal physiologic conditions the difference between arterial PCO_2 (from ABG) and alveolar PCO_2 ($ETCO_2$ from capnography) is 2–5 mmHg. This difference increases in ETT dislodgment or leak, ARDS, and a leak in the capnography system.
- Capnography is an important tool during cardiac arrest. An $ETCO_2$ measurement less than 10 mmHg suggests poor chest compression quality or a terminal cardiac arrest. A sharp rise in $ETCO_2$ is often the earliest indicator of ROSC.
- The accuracy of capnography in detecting esophageal intubation during cardiac arrest is not certain.

Arterial blood gases

- ABG analysis is one of the most useful laboratory tests in monitoring and managing critically ill patients with respiratory and metabolic disorders.
- Provides pH, $PaCO_2$, and PaO_2 measurements which allow assessment of oxygen tension, saturation, A-a gradient, ventilation, and acid–base disorders.
- The radial artery site is the preferred site to obtain arterial blood since it has the best collateral circulation and it is very superficial at the wrist; although this can be difficult in obese or hypotensive patients.
- ABG instruments measure pH, PCO_2, and PO_2. The bicarbonate and oxyhemoglobin saturation values are calculated.
- The gap between SaO_2 on ABG and SpO_2 by pulse oximetry should be less than 5%.
  - If the SpO_2 is higher – consider methemoglobin or carboxyhemoglobin.

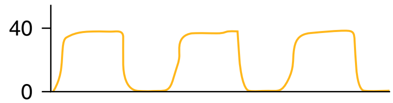
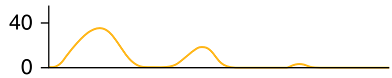
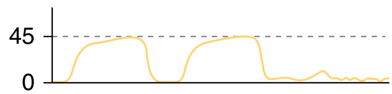
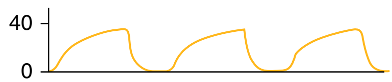
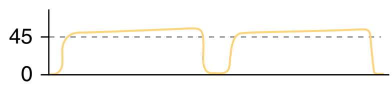
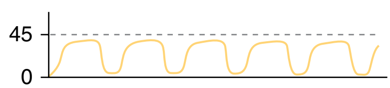
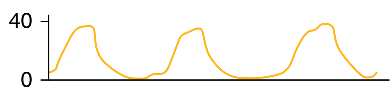
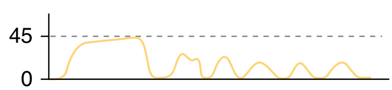
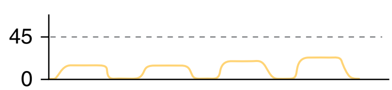
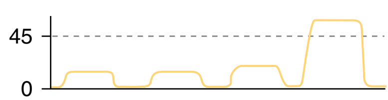
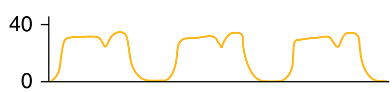
Indications for ABG

- To measure arterial gas tensions and efficacy of oxygenation and ventilation.
- Diagnosis of acute/chronic respiratory failure.
- Allows estimation of A-a gradient.
- Assessment of response to oxygen therapy, mechanical ventilation, and non-invasive ventilation.
- Assessment of metabolic state.
- Comparison of oxygen saturation using pulse oximetry when carboxyhemoglobinemia and methemoglobinemia are suspected.
- In state of circulatory shock and severe hypothermia when pulse oximetry is not reliable.

Cautions with ABG

- If there is delayed analysis of the sample, consumption of O_2 and production of CO_2 continues in the syringe.
- Obtain ABG 10–20 minutes after a change in oxygen therapy.
- Air contamination with large air bubbles in the sample may increase PaO_2 and decrease $PaCO_2$.
- Poor drawing technique including accidental venous puncture.
- States of hyperpyrexia or hypothermia may shift the oxyhemoglobin curve. Adjustment of ABG for temperature is generally not needed (especially for Ph and $PaCO_2$).
- Excessive heparin may decrease the bicarbonate and $PaCO_2$. Heparin must be discarded and then at least 2 mL of blood should be obtained.
- In patients with leukemia, white blood cells may consume O_2 in the specimen and lead to a falsely low PaO_2.

Table 20.2 Interpretation of capnographs.

Clinical uses	Waveform	Interpretation
Intubation		
Endotracheal		Normal waveform
Esophageal		$PETCO_2$ = 0 or low Short lived capnogram of decreasing height
Tube dislodgment Disconnection		Sudden loss of waveform $ETCO_2$ =0
Mechanical ventilation		
Airflow obstruction, e.g. bronchospasm		No alveolar plateau 'Shark fin'
Hypoventilation		RR ↓ $ETCO_2$ ↑
Hyperventilation		RR ↑ $ETCO_2$ ↓ Decreased amplitude and width
Circuit problems		
Leak ET tube small for airway		Blunted alveolar plateau
Kinked ET tube Hypopharyngeal partial obstruction		
Cardiopulmonary arrest		
CPR ineffective		$ETCO_2$ <10 mmHg
ROSC		Abrupt ↑ $PETCO_2$ >40 mmHg at ROSC
Sedation		
Muscle paralytics		Paralytics wearing off Spontaneous breath during mechanical ventilation

Use of venous blood gases

- Central venous blood gas $ScvO_2$ has been used to guide resuscitation during severe sepsis/shock. Normal $ScvO_2$ (from an internal jugular or subclavian vein) is >70%.
- Peripheral venous blood gas is of limited value as it is more representative of local than central venous O_2. It can be used along with SpO_2.

- A low $ScvO_2$ may indicate:
  - Cardiac output is inadequate to meet tissue oxygen needs.
  - Hemoglobin is low.
  - SaO_2 is low.
  - Oxygen consumption has increased without an increase in oxygen delivery.

Comparison of arterial blood gas and venous blood gas

Arterial blood gas (ABG)	Venous blood gas (VBG)	Comments
Measure of oxygenation and ventilation **Normal values** pH 7.35–7.45 PCO_2 35–45 PO_2 80–100 HCO_3 22–26 **Advantages** ABG is more accurate in hemodynamically unstable patients ABG is more accurate when lactic acid (LA) >2 mmol	Measure of ventilation and perfusion pH 7.31–7.41 PCO_2 40–50 PO_2 35–40 HCO_3 22–26 Regular venipuncture or drawn from central venous catheter	May be useful in the hemodynamically stable patient Technical consideration is that VBG correlats with ABG when <1 minute of tourniquet time
Disadvantages Painful Pseudo-aneurysm formation AV fistula	Does not measure PO_2 Inaccurate when PCO_2 >44 mmHg Limited for LA >2 mmol	Values do not correlate in the state of low perfusion, where ABG is preferred Equivocal results of VBG should be confirmed with ABG

CLINICAL PEARLS

- Failure of machine calibration may give spurious ABG results.
- Excessive heparin in the ABG syringe may decrease the bicarbonate and $PaCO_2$. Heparin must be discarded before the sample is taken.
- States of hyperpyrexia or hypothermia may shift the oxyhemoglobin curve. ABGs are reported at ideal body temperatures as blood gas analyzers warm blood to 37°C. It is not necessary to correct ABG for body temperature.
- Extreme elevation of leukocytes or platelets (e.g. hematologic malignancies) may vigorously consume the dissolved oxygen from an ABG specimen. The ABG specimen must be analyzed immediately, such as in a point-of-care analyzer. Pulse oximetry or point-of-care ABG is the method of choice for oxygenation assessment when this effect is suspected.

Co-oximetry

- Co-oximetry is performed on an ABG when methemoglobinemia or carboxyhemoglobinemia is suspected.
- Technique measures wavelengths of light, which determines the percentages of the various forms of hemoglobin, in relation to total hemoglobin. These forms include oxygenated, deoxygenated, carboxy- and methemoglobin.

- SpO_2 = Oxy – Hb/[(Oxy – Hb) + (Deoxy – Hb)] – [(CO – Hb) + (Met – Hb)].
- Co-oximeters are mostly free of the artifacts that are encountered with pulse oximeters.

CLINICAL PEARLS

- Co-oximetry can be used to diagnose possible toxic exposure leading to abnormal hemoglobin.
- Pulse oximetry may be inaccurate in these situations:
  - Carboxyhemoglobinemia: the pulse oximeter reads falsely high saturation, as carboxyhemoglobin absorbs at the same wavelength of light.
  - Methemoglobinemia: pulse oximetry reads falsely low. Suspect when the PaO_2 is normal and the patient is cyanotic.

Lung mechanics on mechanical ventilation

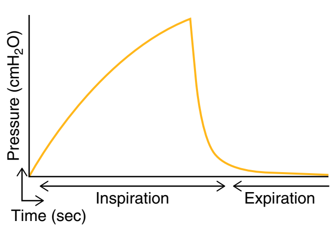
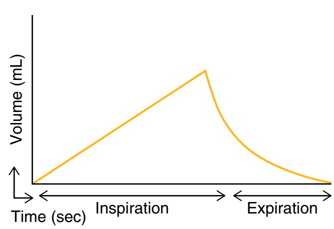
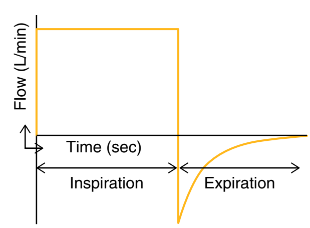
Respiratory monitoring on mechanical ventilation is reviewed in detail in Chapter 21.

BOTTOM LINE

- Ventilator waveform analysis is of the utmost importance for the monitoring and management of a mechanically ventilated patient.
- The routine parameters displayed are waveforms of volume, pressure, and flow over time, where time is the x-axis.
- The pressure–volume loop is a construct to understand the factors of lung recruitment and over-distention and is not generally used for clinical decisions.

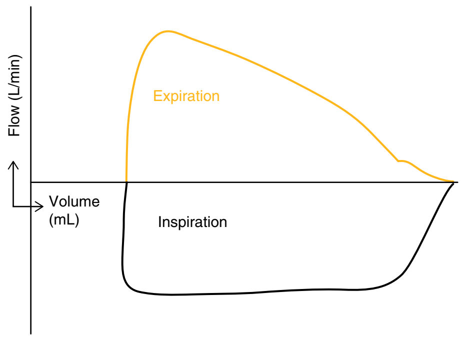
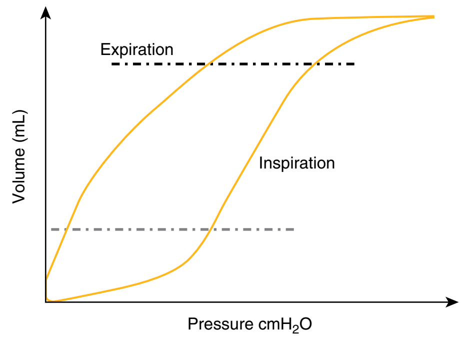
Ventilator waveforms

Important information can be derived from the ventilator waveforms:

Pressure/time	Volume/time	Flow/time
		
Breath type distinction Triggering effort Air trapping Respiratory mechanics (C/Raw) Plateau pressure Peak flow (VC) Asynchrony Lung mechanics Rate I:E ratio	Air trapping/auto-PEEP Leaks Adequate tidal volume Active expiration Asynchrony	Air trapping/auto-PEEP Airway obstruction Airway resistance Bronchodilator response Active expiration Inspiratory flow Flow starvation Triggering effort Asynchrony

Ventilator loops

Important information can also be derived from the ventilator loops:

Flow–volume loop	Pressure–volume loop
	
Airway trapping Airway obstruction Airway resistance Bronchodilator response Inspiratory/expiratory flow Leaks Water or secretion accumulation Asynchrony Tracheomalacia	Lung over-distention – 'beaking' Airway obstruction Work of breathing Leaks Triggering effort Respiratory mechanics Bronchodilator response

Pressure–volume loop

The pressure–volume loop is a theoretical construct and is not measured directly (Figure 20.2). It is currently not recommended that ventilator settings are based on the pressure–volume curve.

- The loop sits at the preset PEEP level (zero if there is no PEEP) and describes the pressure–volume relationship during inspiration and expiration.
- The lower inflection point at the beginning of inspiration: the point at which the lung begins to open. This is the point of minimal pressure adequate for alveolar recruitment. Setting PEEP above this point theoretically prevents alveolar de-recruitment with each breath.
- Upper inflection point at the end of inspiration: past this point, an increase in pressure does not result in a further increase in volume, but in alveolar over-inflation and alveolar damage.

Important parameters to monitor on mechanical ventilator

Positive end-expiratory pressure (PEEP) and auto-PEEP

- Increases functional residual capacity (FRC) by recruiting collapsed alveoli.
- The purpose of PEEP is to increase the volume of gas remaining in the lungs at the end of expiration in order to decrease the physiologic shunting of blood and improve gas exchange.
- Auto-PEEP indicates the presence of positive pressure at the end of expiration due to air trapping. Auto-PEEP can occur due to time or flow limitation. Auto-PEEP is not displayed as PEEP on the usual ventilator graphics.

How to identify auto-PEEP on the graphics

- Expiratory flow does not return to baseline before the next breath begins (Figure 20.3).

Airway pressures and airway resistance

- Peak inspiratory pressure (PIP) is the pressure needed to deliver a tidal volume breath and overcome the elastic and airway resistance. Without lung disease, PIP is only slightly above the plateau pressure.
- Plateau pressure (P_{plat}): measurement of the airway pressure at the end of inspiration, during an inspiratory pause.

How to identify increased resistance to inspiration on the waveform

- Pressure wave: PIP increases while the plateau is stable (Figure 20.4).

Lung compliance

- Compliance reflects the ease of distensibility of the lungs/chest wall system.
- Lung compliance is dynamic (peak pressure) when airflow is present or static (plateau pressure – no airflow).

How to identify changes in compliance on the waveform

- Decreased compliance: pressure wave – PIP and plateau pressures increase.
- Increased compliance: pressure wave – PIP and plateau pressures decrease.

CLINICAL PEARLS

- High peak pressure and high P_{plat}: consider pulmonary edema, consolidation, pneumothorax, pleural effusion, ARDS, atelectasis, main stem intubation, tension pneumothorax, peritoneal gas insufflation, and intra-abdominal compartment syndrome,
- High peak pressure but low to normal P_{plat} implies increased airway resistance: consider bronchospasm, mucous plug, secretions, obstructed or kinked endotracheal tube, or biting endotracheal tube. Monitor change after beta-agonist therapy.
- Very low peak pressure and low plateau pressure: consider disconnected tubing or lost airway.

Monitoring respiratory muscle strength

- Assessing respiratory muscle strength is essential for neurologic patients and patients with chronic critical illness.
- Causes of reduced respiratory muscle strength include diseases of the chest wall, pleura, lung parenchyma, nerves, muscles, and abdominal distension.
- Vital capacity (VC) and maximal inspiratory pressure are the two most commonly used values for bedside assessment of respiratory muscle strength.
- Bedside measurements are notoriously inaccurate but are more useful when repeated to establish a trend.

Vital capacity

- This is the maximum amount of air that can be exhaled after a maximum inspiration.
- It is effort dependent, reflects the mechanical function of both inspiratory and expiratory muscles, and provides an indication of the patient's ability to inspire deeply, maintain lung expansion, and cough.
- Normal VC is 65–75 mL/kg and the normal VT (tidal volume) is 7 mL/kg (about 500 mL). In general a VT of 5 mL/kg or a VC <15 mL/kg is indicative of serious respiratory muscle dysfunction.
- A VC <10–15 mL/kg may require mechanical ventilator support (invasive or non-invasive).

Maximal inspiratory pressure

- Measured during a maximum inspiratory effort that is sustained for ≥1 second against an occluded airway at residual volume or FRC.
- It is effort dependent.
- Maximum inspiratory and expiratory pressures can be measured at the mouth or via an endotracheal/tracheostomy tube.
- The normal value for maximal inspiratory pressure varies with age and sex, exceeding −90 cmH_2O in young females and −130 cmH_2O in young males. More negative is better.
- Less negative than −20 to −25 cmH_2O suggests that the patient is unlikely to be able to sustain adequate spontaneous ventilation.

Monitoring diaphragmatic function

- Diaphragmatic dysfunction is a well-described ventilator-associated injury but commonly under-recognized in the ICU. Suspect diaphragmatic dysfunction in patients who have failed weaning and have unexplained ventilator dependency.
- Assessment of suspected diaphragm dysfunction utilizes several modalities. Individual methods such as chest radiograph have low sensitivity (90%) and specificity (44%).

Causes of diaphragmatic dysfunction

- Prolonged ICU course. Contributing factors include neuromuscular-blocking agents, glucocorticoids.
- Critical illness myopathy.
- Critical illness polyneuropathy.
- Cervical spine C1–C4 injury.
- Flail chest.
- Neuromuscular diseases: multiple sclerosis, Guillain–Barré syndrome, amyotrophic lateral sclerosis, myasthenia gravis, traumatic brain injury, muscular dystrophy, paraneoplastic syndromes.
- Pulmonary disorders: ARDS, ventilator-associated diaphragmatic injury, hyperinflation due to COPD and asthma.

Assessment of diaphragm dysfunction

Diagnostic method	Parameters
Bedside exam	Abdominal/thoracic paradox Bedside spirometry
CXR	Diaphragm position, unilateral, bilateral Elevated hemi-diaphragms Bibasilar or unilateral atelectasis
Ultrasonography	B-mode: assesses diaphragm thickness and motion M-mode (curvilinear probe): may assess the amplitude of diaphragmatic movement towards the US probe
Vital capacity	The reduction in VC is more apparent on the supine measurement

CLINICAL PEARLS

- Facial weakness from stroke and lack of teeth may prevent good seal and therefore may lead to inaccurate measurements.

Imaging in respiratory monitoring

Chest radiograph

- Chest radiographs are indicated to evaluate a change in clinical condition, course of illness, or to follow catheter and tube placement.
- Routine daily chest radiographs in the ICU are not generally indicated.

Goal-directed lung ultrasonography

As ICU physicians become more proficient in point-of-care ultrasonography, ultrasound may replace CXR in certain aspects of critical care.

- US is a widely available, inexpensive, accurate bedside diagnostic tool.
- It is operator dependent.
- In the right clinical setting US gives immediate clues:
  - A-lines and lung sliding point to normal lung aeration.
  - Seashore sign. Lung sliding in M-mode: excludes pneumothorax. Barcode/stratosphere sign in M-mode: pneumothorax cannot be excluded.
  - B-lines suggest pulmonary edema, either increased hydrostatic pressure pulmonary edema or ARDS.
  - Lung hepatization, hyperechoic punctiform images, or sonographic air bronchograms suggest lung consolidation.
  - Pleural effusion recognition, simple or with loculation.
  - Echocardiogram showing right ventricular dilation and hypokinesis which spares the apex may suggest pulmonary embolism (McConnell's sign).

Reading list

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Williams AJ. Assessing and interpreting arterial blood gas and acid-base balance. BMJ 1998;317(7167):1213–16.

Images

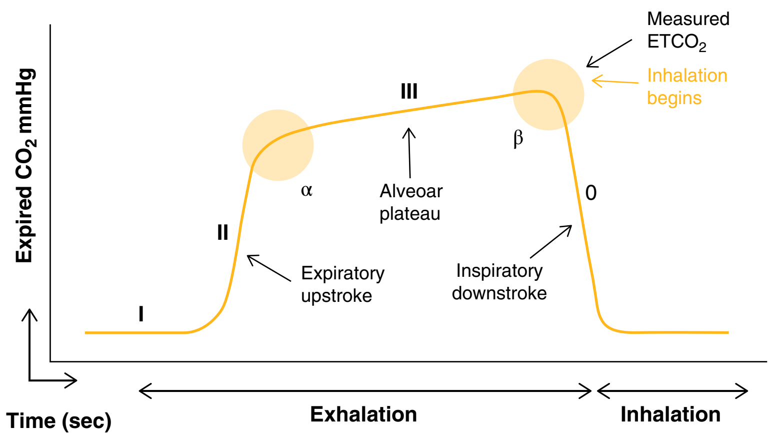

Figure 20.1 The normal capnograph.

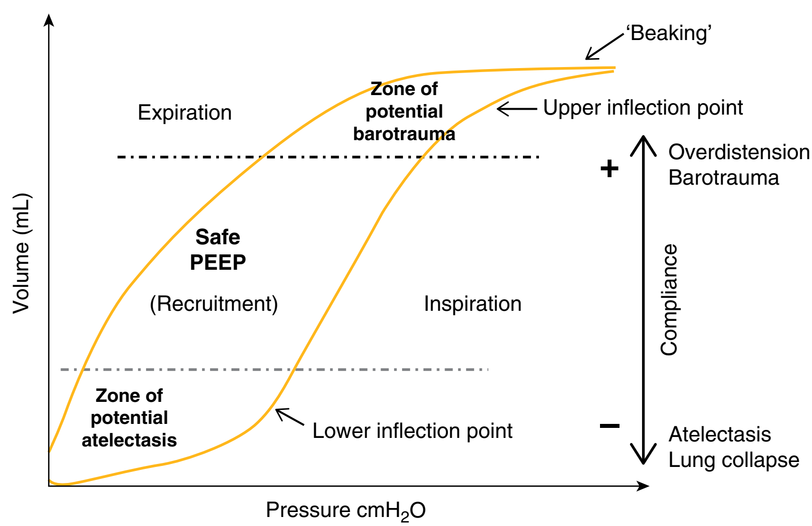

Figure 20.2 Inflection points in pressure–volume loops.

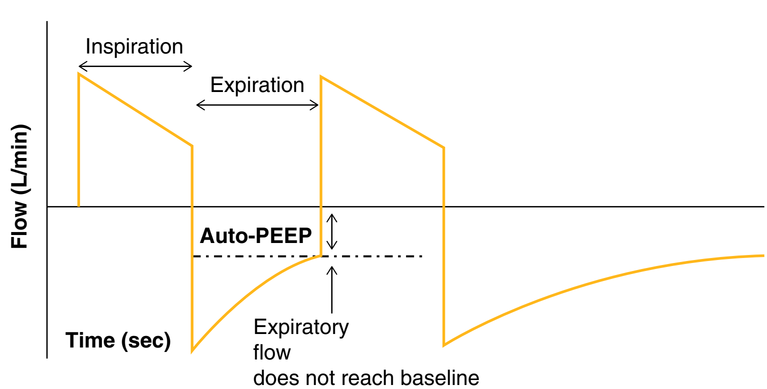

Figure 20.3 Pressure flow versus time waveform demonstrating increased resistance to inspiration.

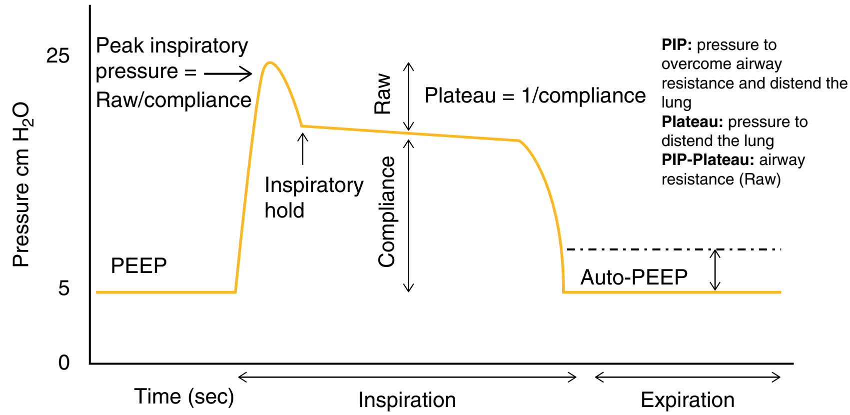

Figure 20.4 Pressure versus time waveform demonstrating increased resistance to inspiration.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 21

Mechanical Ventilatory Support

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OVERALL BOTTOM LINE

- Invasive mechanical ventilation is initiated for hypoxemic respiratory failure, hypercapnic respiratory failure, and airway protection.
- Understanding the different modes and phases of ventilation is important in order to facilitate ventilator–patient synchrony and to reach desired therapeutic endpoints.
- Low tidal volume ventilation has been demonstrated to reduce mortality in ARDS.
- Dynamic hyperinflation and auto-PEEP in obstructive airways diseases can be mitigated by utilizing a low respiratory rate and permissive hypercapnia.
- The effect of positive pressure ventilation on cardiovascular performance is complex and important to understand to minimize paradoxical worsening of cardiac and respiratory system functions when positive pressure ventilation is applied.
- A systematic approach is required for evaluating respiratory deterioration in a patient on mechanical ventilation support.

Background

Definition and goals of invasive mechanical ventilation

- Mechanical ventilation is the process by which a patient's respiratory requirements are partially or completely supported by a mechanical ventilator.
- The primary purpose of mechanical ventilation is to optimize oxygenation and CO_2 removal.
- The ventilator takes over the work of breathing fully or partially. The ventilator plays an essential role in relieving the systemic effects of respiratory distress, including an increase in oxygen demand by the respiratory muscles and the myocardium. This elevated work of breathing can result in myocardial ischemia and the production of lactate.
- In non-invasive ventilation, positive pressure is delivered through a non-invasive interface to the patient's mouth or nose.
- In invasive ventilation, the ventilator is connected to a conduit that bypasses the anatomic upper airways and delivers air directly into the trachea. This can be done through a nasotracheal, endotracheal, or tracheostomy tube.
- This chapter will explain invasive mechanical ventilation.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Prevalence and impact

- A large retrospective study of over 6 million hospitalizations found that 2.8% of the patients received mechanical ventilation and the in-hospital mortality was 34.5%.

Indications for invasive mechanical ventilation

- Hypoxemic respiratory failure (Table 21.1).
- Hypercapnic respiratory failure (Table 21.1).
- Protection of airways and lung parenchyma:
  - For patients at risk of aspiration.
  - Maintenance of airway patency, such as with expanding neck lesions or airway edema.

Commonly used terms

- *Predicted body weight* (PBW): calculated weight used for weight-based ventilator settings. It is based on gender and height, accounting for the fact that lung size and capacity will remain the same despite variations in a patient's weight over time.
  - Men: PBW = 50 kg + 2.3 kg × (height (inches) – 60).
  - Women: PBW = 45.5 kg + 2.3 kg × (height (inches) – 60).
- *Tidal volume* (V_T): volume of air delivered to the patient per breath. It is expressed in milliliters (mL). Recommended V_T for mechanically ventilated patients: lung protective ventilation ≤8 mL/kg PBW; ARDS settings ≤6 mL/kg PBW.
- *Respiratory frequency* (*f*): number of breaths delivered per minute. Often ranges between 12 and 20/min. Patients with metabolic acidosis usually need a higher rate, whereas those with obstructive disease should be ventilated with lower rates.
- *Fraction of inspired oxygen* (FiO_2): concentration of O_2 in the inspired gas. It ranges from 0.21 (room air) to 1.0 (100% O_2). FiO_2 is titrated to maintain a SpO_2 of ≥90%, or a PaO_2 of ≥60 mmHg. An FiO_2 higher than 60% can result in oxygen toxicity.
- *Positive end-expiratory pressure* (PEEP): set amount of positive pressure in cmH_2O that is maintained at the end of expiration. This can be extrinsic or intrinsic. A baseline extrinsic PEEP of 5 cmH_2O is frequently used to prevent atelectasis.
- *Minute ventilation* (V_E): volume of air exchanged in 1 minute. V_E is the product of tidal volume and respiratory frequency $V_E = (V_T \times f)$, expressed in liters per minute (L/min). Range: 5–10 L/min; this can be higher in patients with high minute ventilation requirements, such as sepsis.
- *Peak inspiratory pressure* (P_{peak}): highest pressure (expressed cmH_2O) recorded during inspiration. It reflects the PEEP, compliance of the lungs/pleura/chest wall system, and the flow resistance of the airways.

Table 21.1 Features of hypoxemic and hypercapnic respiratory failure.

Respiratory failure	Mechanisms	Examples
Hypoxemic	Ventilation–perfusion mismatch Impaired diffusion Right-to-left shunt Hypoventilation	Pneumonia Cardiogenic pulmonary edema Pulmonary embolism ARDS Pneumothorax
Hypercapnic	Decreased minute ventilation Increased dead space ventilation Increased CO_2 production Venous admixture	Sedative overdose CNS injury Neuromuscular disease Severe asthma COPD

- *Plateau pressure* (P_{plat}): pressure resulting from the elastic recoil of the lung and chest wall at the end of inspiration when the system has reached a no gas flow state. It is assessed by applying a short pause during inspiration. Plateau pressure is also affected by the pleura/chest wall system.
- *Mean airway pressure* (P_{aw}): time-weighted average pressure during a respiratory cycle.
- *Compliance* (C_L): ease with which the lungs can distend. It is the quotient of the change in volume and the change in pleural pressure ($C_L = \Delta V/\Delta P$) and is expressed in L/cmH_2O.
- *Static compliance* (C_S): compliance measured in conditions of no gas flow; $C_S = V_T/(P_{plat} - \text{PEEP})$.
- *Dynamic compliance* (C_D): compliance measured during gas flow and therefore affected by resistance; $C_D = V_T/(P_{peak} - \text{PEEP})$.
- *Airway resistance* (R_{insp}): resistance to airflow during inspiration. It is determined as the ratio of the pressure gradient needed to overcome airways resistance ($P_{peak} - P_{plat}$) and the inspiratory flow rate (V_{insp}); $R = (P_{peak} - P_{plat})/V_{insp}$.
- *Inspiratory time* (T_I): time in seconds required to deliver V_T at a specified flow rate ($T_I = V_T$/flow). A longer Ti increases the P_{aw}. A shorter T_i delivers V_T faster.
- *Inspiratory rise time*: time in seconds required to reach the set peak inspiratory pressure. It can be adjusted to match patient effort. For patients with high V_T demand the rise time can be shortened.
- *Inspiratory flow rate* (V_{insp}): rate at which gas is delivered to the patient's lungs during the inspiratory phase (expressed as L/min). This is normally set at 40–100 L/m. A higher V_{insp} delivers V_T faster and shortens inspiratory time.
- *Trigger sensitivity*: level of spontaneous effort needed to trigger a machine breath. This can be set based on flow or pressure thresholds. Typical settings are –2 cmH_2O or 50% change of bias flow.
- *Autocycling*: ventilator breath is initiated in absence of patient respiratory effort or set rate. This can be due to a leak in the system, such as a faulty exhalation valve or damaged ventilator tubing.
- *I:E ratio*: inspiratory to expiratory time ratio. Depends mainly on respiratory rate; inspiratory time has less impact. Inspiration time is normally shorter than expiratory time, at least 1:3. In airflow obstruction, it takes longer for the expiration phase, and so a longer I:E ratio is desired.

Setting the ventilator

The clinician must set the parameters listed here, based on the indication for mechanical ventilation, the patient's underlying clinical condition, and defined therapeutic endpoints.

- *Mode*: the mode of mechanical ventilation refers to the shape of the inspiratory pressure or flow characteristics and will determine if a patient can augment the V_T or respiratory rate using his or her own efforts. Modes are usually volume pre-set or pressure pre-set. For most patients, an assist control mode is used. A mode such as volume control or pressure-regulated volume control (PRVC) is most commonly used to assure desired tidal volume. Weaning from mechanical ventilation is often performed using pressure support mode. (See explanation of modes later.)
- *Tidal volume*: The tidal volume V_T is determined by the predicted body weight and generally set at 6–8 mL/kg PBW.
- *Respiratory rate*: the respiratory rate is set based on the clinical indication for mechanical ventilation. For patients with sepsis, metabolic acidosis, or conditions with high minute ventilation requirements, it is set at a higher rate of 20/min. Patients with ARDS ventilated with low tidal volumes may need an even higher rate. In obstructive disease, a low rate of 10–12/min is set to allow sufficient time for exhalation.
- *FiO_2*: The FiO_2 is initially set at 100% and titrated down to maintain oxygen saturation of 90% at the lowest possible FiO_2.
- *PEEP*: this is often initiated at 5 cmH_2O. PEEP is set at higher levels in disease such as ARDS, when implementing 'open lung strategy' to provide adequate oxygenation and prevent atelectasis.

Ventilator phases

There are three phases in a ventilatory cycle: what starts the breath, what is the goal that must be reached, and how the breath ends so that expiration can occur.

Trigger

This is the phase in which the breath is initiated. There are three basic types of triggers:
- Time: a breath is delivered at a set frequency per minute.
- Pressure: a breath is delivered when the ventilator senses patient effort in the form of negative pressure.
- Flow: a breath is delivered when the ventilator senses patient effort in the form of a decrease in flow. Flow triggering reduces the effort required from the patient and is the most commonly used trigger variable.

Limit

This is the phase in which a positive pressure breath is delivered that is governed by a set limit. The limit is the variable that needs to be reached and maintained before inspiration ends. While the limit cannot be exceeded, it does not terminate the inspiratory cycle. There are three commonly used limit variables:
- Pressure: a set pressure is targeted during inspiration. Flow and volume are variable and dependent on the lung compliance and airway resistance.
- Flow: a set flow is targeted. Airway pressure is variable and dependent on the lung compliance and airway resistance.
- Volume: a set tidal volume is targeted.

Cycle

This is the phase in which inspiration ends and the breath cycles from inspiration to expiration.
- Volume cycled: breath cycles from inspiration to expiration after a pre-set tidal volume is met (i.e. volume control ventilation).
- Time cycled: breath cycles from inspiration to expiration after a prespecified inspiratory time (i.e. pressure control ventilation).
- Flow cycled: breath cycles from inspiration to expiration after inspiratory flow decreases to a prespecified level (i.e. pressure support ventilation).
- Pressure cycled: during volume control ventilation, breath cycles from inspiration to expiration if airway pressure exceeds the set limit regardless of the volume delivered.

Modes of mechanical ventilation

- The modes of mechanical ventilation are best separated into full ventilatory support modes and partial ventilatory support modes. In full ventilator support modes, there are mandatory breaths that are set to ensure the minimum minute ventilation. Partial support modes such as pressure support are patient triggered, provide varying ventilatory support, and are often used for weaning from mechanical ventilation.
- Assist control refers to patient-triggered breaths which are assisted during full ventilator support. The ventilator delivers mandatory breaths and the patient has the option of triggering additional breaths that are assisted by the ventilator and have exactly the same control parameters as the mandatory breaths.
- The common ventilator modes are listed in Table 21.2.

Volume control (VC)

- Commonly used mode.
- The tidal volume is set and guaranteed. This results in a consistent minute ventilation regardless of the lung resistance, compliance, or of the patient's ability to contribute to the breathing effort.
- While this may be beneficial in patients with hypercapnic respiratory failure requiring controlled and efficient ventilation, it may be detrimental to patients with increased resistance or decreased compliance as it can lead to higher airway pressures.

Table 21.2 Common ventilator modes.

Full ventilatory support	Partial ventilatory support
Volume control	Pressure support
Pressure control	Volume support
Pressure-regulated volume control	

- The breath is flow targeted and volume cycled. Since flow is the limit variable, it remains constant throughout inspiration. Since volume is the cycle variable, inspiration ends after delivery of the set tidal volume.
- The clinician usually sets the *f*, V_T, inspiratory flow rate, flow waveform, FiO_2, and PEEP.
- Advantages: guaranteed minute ventilation.
- Disadvantages: patient dyssynchrony and difficulty controlling the plateau pressure.

Pressure control (PC)

- A constant pressure is delivered throughout inspiration. The delivered volume will therefore vary depending on the patient's lung compliance and airway resistance.
- The breath is pressure targeted and time cycled. Since pressure is the limit variable it remains constant throughout inspiration. Since time is the cycle variable, inspiration ends after predetermined time.
- The clinician sets the *f*, inspiratory pressure, T_I, FiO_2, and PEEP.
- Initial settings:
  - *f*: 12–14 breaths/min.
  - Inspiratory pressure: 20–24 cmH_2O, not to exceed 30 cmH_2O, and titrated to achieve tidal volumes of 6–8 mL/kg PBW.
  - T_I: 0.9–1.0 seconds.
  - FiO_2: 100%.
  - PEEP: 5 cmH_2O.
- Advantages: patient comfort, decelerating flow pattern, plateau pressure can be regulated, and can be used with cuffless endotracheal tube.
- Disadvantages: tidal volume is not guaranteed.

Pressure-regulated volume control (PRVC)

- Commonly used mode.
- Dual control pressure ventilation mode. It is a variant of pressure controlled ventilation but resolves the disadvantage of variable tidal volumes (due to changes in lung characteristics over the respiratory failure course) by adjusting the delivered pressure on a breath by breath basis to reach a set tidal volume. The ventilator uses the P_{plat} to provide the desired tidal volume using the lowest possible pressure.
- There are two unique features:
  - It does not allow the pressure to rise above a level set at 5 cmH_2O below the pressure alarm limit. If that pressure is reached, the breath automatically cycles off to expiration.
  - Decelerating flow pattern.
- Advantages: decreases the risk of barotrauma, decreased work of breathing, improved gas distribution, and decreased airway resistance.
- Disadvantages: may worsen auto-PEEP since the flow is decelerating and in effect prolonging inspiratory time. It may not provide adequate flow for patients who are flow starving, thus increasing work of breathing. May result in very variable tidal volumes if the patient intermittently makes a significant inspiratory effort. If there are inherent leaks in the system (such as loss of volume due to chest tubes), the device may not be able to obtain the P_{plat} and this will cause the mode to autocycle, leading to dyssynchrony.

Pressure support (PS)

- Mode in which all breaths are triggered by the patient. It can only be used for patients who are breathing spontaneously.
- Pressure limited and flow cycled. Since the breath is pressure limited, a constant pressure is maintained throughout inspiration. Since it is flow cycled, the ventilator continues to deliver the breath until the inspiratory flow has decreased to a specific level (e.g. 25% of the peak inspiratory flow), and expiration then follows. The delivered tidal volume depends on the patient's lung compliance and airway resistance.
- The clinician sets the inspiratory pressure, sensitivity, PEEP, and FiO_2.
- Tidal volumes are variable and dependent on lung compliance and resistance and respiratory muscle strength.
- This mode is often used for weaning from mechanical ventilation.
- Advantages: facilitates weaning, less sedation is needed, and improved patient comfort.
- Disadvantages: needs close monitoring and tidal volumes are variable.

Volume support (VS)

- Mode similar in concept to PRVC. Each breath is pressure supported to attain a volume target.
- The breath is patient triggered, pressure limited, and flow cycled. The pressure support for each breath is calculated by the compliance measured during the previous breath.
- As the patient is recovering and making sufficient respiratory efforts, the amount of pressure support provided will decrease.
- Advantages: guaranteed minimum tidal volume and patient comfort.
- Disadvantages: potential for dyssynchrony.

Synchronized intermittent mandatory ventilation (SIMV)

- The ventilator delivers a set number of mandatory breaths while still allowing the patient to take spontaneous breaths. The mandatory breaths can be any of the previously mentioned control modes (i.e. VC, PC, PRVC). The spontaneous breaths can be pressure supported.
- Advantages: by progressively decreasing the frequency of the mandatory breaths, it was theorized that this mode would allow reconditioning of patients' respiratory muscles and accelerate weaning.
- Disadvantages: large trials have shown this mode to prolong weaning compared with weaning using pressure support mode or T-piece.

Airway pressure release ventilation (APRV)

- Generally a rescue mode for severe hypoxemic respiratory failure.
- Variant of bilevel ventilation in which a relatively high airway pressure P_{high} is maintained for a prolonged period with brief time of pressure at a lower level P_{low}. The inflation of the lung is allowed by the time spent at P_{high}. Then the brief exhalation is followed by inflation again.
- Initial settings:
  - P_{high}: 30 cmH_2O.
  - P_{low} (PEEP): 0 cmH_2O.
  - T_{high}: 4 seconds.
  - T_{low}: 0.5 seconds.
  - FiO_2: 100%.
  - Pressure support: 5 cmH_2O (if patient is triggering breaths).
- Advantages: inflation pressures are maintained thus promoting lung recruitment, which has theoretical advantages in conditions such as ARDS. It is also a lung protective mode as the set pressures cannot be exceeded. Patient is able to breath spontaneously thus decreasing the need for heavy sedation.

- Disadvantages: ventilation occurs only in the limited time of low pressure P_L which can result in hypercapnia. Tidal volumes can be higher than the target low tidal volume ventilation. There is also a risk of barotrauma due to auto-PEEP.

Troubleshooting the ventilator

The ventilator is a life-sustaining device. A malfunction or impairment of gas exchange due to the ventilator or the patient's own disease can lead to a rapid and fatal patient decompensation. It is therefore essential to understand the ways by which the ventilator or the circuit can fail and how to identify problems.

High pressure alarm

- Indicates an elevated airway pressure. Airway pressures may be elevated due to the underlying respiratory disorder, but also for reasons such as the patient coughing or biting the endotracheal tube, as well as partial or complete occlusion of the endotracheal tube.
- An assessment of the peak pressure and the plateau pressure can help identify the etiology if not evident on examination, with the pressure gradient between peak inspiratory and plateau pressures being proportional to the airways flow resistance.
- Increased P_{peak} with normal P_{plat}: consider obstructive processes (high pressure gradient):
  - Obstructive airways disease.
  - Patient–ventilator dyssynchrony.
  - Tube obstruction secondary to secretions.
- Increased P_{peak} with increased P_{plat}: decreased lung/chest wall compliance (normal pressure gradient):
  - Pneumothorax.
  - Abdominal compartment syndrome.
  - Pneumonia.
  - Atelectasis.
  - ARDS.
  - Cardiogenic pulmonary edema.
  - Auto-PEEP.

Low pressure alarm (with low tidal volume)

- Indicates a leak somewhere in the patient–ventilator circuit.
- The clinician should always suspect and investigate the following:
  - Air leak due to deflated or damaged cuff.
  - Tube displacement or extubation.
  - Patient disconnection from the ventilator.

Systematic approach to respiratory deterioration in an unstable, mechanically ventilated patient

- Listen to the lungs bilaterally for wheezing, or asymmetric reduced breath sounds, which could indicate a pneumothorax or atelectasis.
- Pass a suction catheter through the endotracheal tube. If it passes easily, this rules out biting, kinking, or obstruction of the tube secondary to secretions.
- Disconnect the patient from the ventilator and manually ventilate. If it is difficult to manually ventilate the patient, this indicates increased airway resistance or decreased compliance. If the patient is very easy to manually ventilate, consider a leak or displaced endotracheal tube.

Disease-oriented settings

ARDS

- ARDS is a complex response to local and systemic inflammation as a result of either direct or indirect injury to the lung. It most commonly arises due to underlying sepsis, aspiration of gastric contents,

pneumonia, multiple transfusions, or trauma. This condition is characterized by non-cardiogenic pulmonary edema, hypoxemia, diffuse alveolar damage, heterogeneous disease distribution, and decreased lung compliance.

- Beside supportive care and treating the underlying cause, mechanical ventilation treatment strategies focus on maximizing ventilator settings to improve hypoxemia and to decrease ventilator-associated lung injury. The landmark ARDSNet study demonstrated that ventilating patients with lower V_T leads to improved mortality.
- While patients on mechanical ventilation are usually started on a V_T of 8 mL/kg PBW, patients with ARDS are started with V_T at 6 mL/kg PBW.
- The respiratory rate needs to be adjusted to compensate for the smaller V_T while maintaining adequate V_E.
- Further adjustment in *f* will be made based on pH assessment from an arterial blood gas, with the goal of maintaining serum pH ≥7.15.
- Perform an inspiratory pause to measure the plateau pressure (P_{plat}). If P_{plat} >30 mmHg, decrease V_T by 1 mL/kg PBW to a minimum V_T of 4 mL/kg PBW. Remember to increase the respiratory rate.
- The PEEP should be increased proportionally to the FiO_2 requirement:

FiO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
PEEP	5	5–8	8–10	10	10–14	14	14–18	18–25

- The Surviving Sepsis guidelines on the management of ARDS in a setting of sepsis include use of low tidal ventilation, titrating plateau pressure to 30 cmH_2O, and use of PEEP.

Obstructive airways disease: status asthmaticus, acute COPD exacerbation

- Obstructive airways diseases such as status asthmaticus and acute COPD exacerbation result in the inability to ventilate adequately. The airflow obstruction prevents full exhalation due to flow and time limitation; air trapping occurs and intrathoracic pressure may rise with resulting dynamic hyperinflation. When severe, this leads to decreased venous return and hypotension. Additionally, the alveolar hypoventilation leads to increased $PaCO_2$ and respiratory acidosis.
- Auto-PEEP refers to PEEP, not set by the clinician, due to incomplete expiration with alveolar air trapping. In obstructive lung diseases, this auto-PEEP is due to expiratory flow limitation from bronchospasm and edema. A rapid respiratory rate can worsen auto-PEEP due to the expiratory time limitation.
- Ventilator settings in patients with acute exacerbation from severe asthma or COPD are geared to optimizing ventilation while preventing auto-PEEP. This is achieved by setting a lower respiratory rate, which allows a favorable I:E ratio and sufficient time for full exhalation.
- Start with a V_T of 8 mL/kg PBW.
- A respiratory rate of 10–12 breaths per minute is a reasonable starting point.
- Monitor for auto-PEEP by monitoring the flow and volume curves to see that expiration is achieved prior to initiation of a new breath. Measure auto-PEEP at end expiration.
- Strategies that improve the I:E ratio and allow longer time for expiration include the following:
  - Decrease the respiratory rate.
  - Decrease the V_T.
  - Increase the inspiratory flow rate.
  - Decrease the inspiratory time.
- Serial arterial blood gases should be performed to monitor for CO_2 retention and respiratory acidosis. Elevated $PaCO_2$ and serum pH as low as 7.15 can be tolerated. This approach is termed permissive hypercapnia.

Cardiovascular effects of mechanical ventilation (heart–lung interactions)

Mechanical ventilation can affect cardiac performance by affecting preload, afterload, and cardiac contractility. The net effect can result in serious hemodynamic consequences, that if not identified and prevented, may complicate the underlying disease management and can worsen clinical outcomes.

Effect on venous return and cardiac output

- Positive pressure ventilation causes a decrease in venous return, resulting in a decrease in preload and possibly a decrease in cardiac output. This effect is accentuated by PEEP and may lead to worsening hypotension, especially in patients presenting with hypovolemia and shock.

Effect on PVR

- PVR
  - PVR is elevated at lung volumes above FRC due to compression of alveolar vessels and at lung volumes below FRC due to tortuous extra-alveolar vessels. PVR is optimal at FRC.
  - PVR increases in severe hypoxemia. Hypoxic pulmonary vasoconstriction develops when regional PaO_2 decreases to less than 60 mmHg.
- High tidal volumes and severe hypoxemia increase PVR. Elevated PVR increases RV afterload, so RV cardiac output may be reduced.

Effect on left heart function

- Positive pressure ventilation may decrease LV afterload which leads to increase in cardiac output.
- Increase in intrathoracic pressure lowers the transmural pressure of the thoracic aorta. The transmural pressure is the difference between the pressure in the vessel and the pleural pressure. The higher intrathoracic pressure decreases the transmural pressure, thus reducing LV afterload and increasing stroke volume.
- In patients with severe heart failure, removal of positive pressure during weaning from mechanical ventilation can lead to decompensation. Transitioning to non-invasive ventilation may be beneficial.

Auto-PEEP

- Auto-PEEP refers to PEEP, not set by the provider, due to incomplete expiration with alveolar air trapping.
- Auto-PEEP can occur due to increased minute ventilation, expiratory flow limitation (COPD, asthma), or expiratory resistance (secretions, patient–ventilator asynchrony).
- Effects of auto-PEEP are due to the increase in intrathoracic pressure. Clinical findings include tachycardia and hypotension.

Complications and prevention

Barotrauma

- Barotrauma is a well recognized complication of mechanical ventilation. It occurs when elevated airway pressures result in damage to the lungs that manifests as extra-alveolar air. This is usually caused by a combination of high tidal volumes and diseased lungs.
- Manifestations of barotrauma are pneumothorax, pneumomediastinum, or pneumopericardium. While some forms of barotrauma require only observation, others require urgent and invasive interventions such as the placement of a chest tube. Patients on positive pressure mechanical ventilation who develop pneumothorax generally require a chest tube.
- Conditions at risk for barotrauma include: ARDS, COPD, and pulmonary fibrosis.

Ventilator-associated events and pneumonia

- A ventilator-associated event (VAE) is defined by the CDC as worsening oxygenation following more than 2 days of increasing FiO_2 or PEEP requirement.
- A VAP occurs after more than 2 days of mechanical ventilation, and requires a change in temperature, WBC, antibiotic administration, and laboratory growth of bacteria. VAP has been demonstrated to increase the mortality of critically ill patients by up to 30%, as well as prolonging the ICU and hospital stay.
- For more detailed information on VAE and VAP, please refer to Chapter 46.
- Ventilator 'bundles' have been developed to prevent VAE and usually include the following measures: elevation of the head of the bed to at least 30°, oral care, endotracheal tube with subglottic suctioning (unsettled), daily assessment for readiness to extubate, and the prevention of stress ulcer bleeding and venous thromboembolism.

Gastric stress ulcer bleeding

- Patients with critical illness undergoing mechanical ventilation are at increased risk for the development of stress ulcers. These can in turn result in life-threatening gastrointestinal bleeding and the need for transfusion of blood products.
- Stress ulcer prophylaxis is initiated for patients with expected mechanical ventilation for more than 48 hours using H_2 receptor antagonists or proton pump inhibitors.

Deep venous thrombosis

- Mechanically ventilated patients are at risk of developing venous thromboembolic events due to venous stasis and a prothrombotic state from the critical illness.
- Pharmacologic prophylaxis is generally initiated using unfractionated or low molecular weight heparin. Intermittent pneumatic compression is also used in most patients.

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Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

with website

CHAPTER 22

Non-Invasive Positive Pressure Ventilation

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OVERALL BOTTOM LINE

- The use of non-invasive positive pressure ventilation (NPPV) in selected patients with acute respiratory failure (ARF) has been shown to reduce endotracheal intubation and associated complications.
- The use of NPPV as initial therapy in acute respiratory failure is rising.
- Patients must be carefully selected and monitored.
- Use of NPPV is associated with reduced mortality in patients with acute exacerbations of COPD.
- NPPV success depends on patient tolerance, which is affected by interface type, ventilator, and settings.
- Patients failing a trial of NPPV should be promptly intubated. Delay in intubation is associated with increase in mortality.
- High flow oxygen therapy via nasal cannula (HFNC) has increasing evidence-based applications in patients with primarily hypoxemic respiratory failure.

Background

- NPPV is defined here as positive pressure ventilation delivered without an endotracheal airway, through a non-invasive interface.
- HFNC is a form of high flow O_2 support. Minimal ventilatory support is provided with this device.
- NPPV support has gained acceptance in the last three decades and its use has increased over time.
- Improved outcomes with specific diseases have been definitively shown.
- Decreased cost has been shown compared with the use of invasive mechanical ventilation.

Principles of action

NPPV

- The positive pressure administered via the non-invasive mask reduces the transthoracic pressure requirements for generating tidal breaths and thereby reduces the work of breathing.
- Improves ventilation and gas exchange by enabling better tidal volumes.
- Allows rest for the respiratory muscles (diaphragm, accessory muscles).
- Decreases left ventricular afterload.
- Decreases right ventricular and left ventricular preload.
- Increases hydrostatic pressures within the alveoli to mobilize pulmonary edema fluid.
- Prevents airway collapse in obstructive lung diseases.
- Maintains upper airway patency (especially during sleep) in patients with obstructive sleep apnea.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Benefits in acute respiratory failure

- Reduces the need for endotracheal intubation.
- Prevents intubation-associated complications (airway trauma, ventilator-associated events).
- Shortens length of stay in the ICU and hospital.
- Improves patient comfort.
- Reduces sedation requirements.

HFNC

- Delivers higher oxygen flow rates via large bore nasal cannula compared with conventional nasal cannula devices.
- In patients with a high respiratory workload, inspiratory flow rates are high and room air is entrained. The high flow rates provided with HFNC lead to less room air dilution of the administered oxygen, therefore higher FiO_2 is delivered.
- Provides a minimal amount of positive pressure secondary to its high flow rates. It has been shown that with the mouth closed, pharyngeal pressure (end-expiratory pressure) increases as flow increases. End-expiratory lung volume is higher.
- Provides good humidification which can reduce airway irritation and improve mucous clearance.
- Decreased anatomic dead space compared with use of NPPV due to increased carbon dioxide washout.

Benefits in acute respiratory failure

- Reduces the need for endotracheal intubation.
- Prevents intubation-associated complications (airway trauma, ventilator-associated events).
- Improves patient comfort.
- Reduces sedation requirements.
- Allows for continuation of activities such as talking and eating.
- Can be used in the presence of secretions.

Indications and contraindications

- NPPV is effective in patients with ARF due to acute COPD exacerbation and cardiogenic pulmonary edema.
- HFNC is emerging as an effective therapy in selected patients with hypoxemic respiratory failure.
- Patients must be carefully selected (Tables 22.1 and 22.2).

Table 22.1 Indications and contraindications for NPPV.

Indications	Contraindications
Ventilatory failure (acute exacerbations of COPD, OHS) Cardiogenic pulmonary edema Acute exacerbation of asthma Post extubation ARF Postoperative ARF Patients at high risk for complications of intubation (older age, obesity) Do not intubate status	Need for emergent intubation Cardiac arrest Respiratory arrest Inability to protect airway due to altered mental status Presence of secretions Sinusitis/otitis media Epistaxis/hemoptysis/hematemesis Ileus/gastric distention Pneumothorax/pneumomediastinum Recent facial trauma or surgery Hemodynamic instability

Table 22.2 Indications and contraindications for HFNC.

Indications	Contraindications
Acute hypoxemic respiratory failure with mild to moderate work of breathing Presence of secretions preventing NPPV use Post extubation	Primary ventilatory failure (hypercapnic failure) Markedly increased work of breathing Respiratory arrest Hemodynamic instability

Basic terminology and settings

- *Mode* (NPPV):
  - Bilevel spontaneous: the set inspiratory/expiratory pressures are delivered with each patient-generated breath. This is the most common mode of NPPV in ARF.
  - Bilevel spontaneous timed (ST): in addition to spontaneous mode, the machine mandates the time for delivery of inspiratory positive pressure, and also a minimum number of mandatory breaths per minute.
  - CPAP: the machine delivers a continuous level of pressure throughout the respiratory cycle (inspiration and expiration).
- *IPAP/EPAP* (NPPV):
  - IPAP is the inspiratory positive airway pressure, defined as the positive airway pressure delivered during the inspiratory phase (as determined by cessation of airflow or maximal inspiratory time). It is usually titrated to achieve a desired tidal volume V_T and ensure adequate ventilation.
  - EPAP is the end-expiratory positive airway pressure. This is analogous to PEEP during mechanical ventilation, and is defined as the pressure delivered during each expiratory phase and during the pause until the next inspiration.
- *Rate* (NPPV):
  - Rate on bilevel mode serves as the backup rate (minimum breaths per minute).
- *Flow rate* (HFNC):
  - The flow rate can be set in liters per minute, and higher flow rates enable the delivery of greater concentrations of O_2, as well as slightly higher positive pressures.
- *FiO_2* (NPPV, HFNC):
  - Both NPPV and HFNC use high flow, closed O_2 delivery systems with an oxygen blender that enable precise titrations of FiO_2, similar to a mechanical ventilator.
- *Patient interfaces* (NPPV, HFNC):
  - While several interfaces are available for NPPV machines, the most commonly used interface in ARF settings is the nasal–oral mask which covers the apertures of both nares and mouth with a tight seal to ensure adequate delivery of FiO_2 and pressures (Figure 22.1).
  - High flow oxygen is most commonly delivered by nasal prongs similar in appearance to low flow nasal cannulas, but with a larger bore to accommodate the higher flow rates (Figure 22.2).

Use of NPPV in disease states

NPPV in acute exacerbation of COPD (AECOPD)

- This is the most common indication for NPPV use with the largest body of evidence.
- Considered first line ventilatory support in patients with AECOPD.
- Strong evidence for:
  - Decreased mortality.
  - Reduced rates of endotracheal intubation.
  - Less treatment failure and faster resolution of clinical symptoms compared with oxygen therapy alone.

  - Reduction in ICU and hospital length of stay and treatment complications compared with invasive mechanical ventilation.
  - More cost effective than invasive mechanical ventilation.
- Can be utilized in the ICU or in closely monitored non-ICU settings.
- Can be used in patients with AECOPD and encephalopathy due to CO_2 narcosis.

NPPV in acute cardiogenic pulmonary edema (CPE)

- There is a robust and growing body of data supporting the use of NPPV in CPE.
- CPAP mode generally first line; patients with concurrent ventilatory failure may benefit from bilevel NPPV.
- Data show improved SpO_2, decreased work of breathing, reduced rates of intubation, and faster clinical improvement.
- Trend towards decreased mortality.
- Contraindicated in patients with cardiogenic shock or altered consciousness.

NPPV in acute exacerbation of asthma

- There is a mixed body of evidence for this indication.
- In early phase of exacerbation can temporize impending respiratory failure by allowing time for medical intervention to work.
- Trend towards quicker reduction in dyspnea, and reduced length of stay.
- No evidence to support reduced rates of intubation or long-term morbidity/mortality benefits.

NPPV in neuromuscular disorders with ARF

- Patients with neuromuscular disease states, whether acute (Guillain–Barré syndrome) or chronic (myasthenia gravis, amyotrophic lateral sclerosis) often present with ARF.
- The use of NPPV in these patients has been shown to reduce the rates of intubation and therefore reduce complications of mechanical ventilation and length of stay.
- Patients with neuromuscular disease in ARF must be watched in a monitored setting with frequent reassessment of respiratory status, since they can worsen and require mechanical ventilation.
- Parameters for monitoring include negative inspiratory force (NIF) and vital capacity. Forced vital capacity (FVC) <20 mL/kg and/or a NIF <30 cmH_2O are considered indications for intubation and mechanical ventilation.
  - Patients meeting these criteria may be monitored closely on NPPV while treatment for the underlying conditions commences; however, they should be promptly intubated if any further deterioration occurs.

NPPV and HFNC in acute hypoxemic respiratory failure

- NPPV had not been recommended for patients with pure hypoxemic respiratory failure, especially those meeting ARDS criteria, for fear of delaying intubation and increasing morbidity and mortality.
- However, there is evidence to support the use of NPPV in immunocompromised patients with hypoxemic respiratory failure.
- NPPV and HFNC are also used for respiratory support in patients with interstitial lung disease in acute respiratory distress with beneficial outcomes including decreased length of stay.
- New studies suggest that HFNC in acute hypoxemic respiratory failure can reduce intubation rates and mortality.
- There are ongoing trials to evaluate whether extubation to HFNC improves outcomes.

Special considerations for NPPV

- *Post-extubation ARF*:
  - Data suggest that NPPV can forestall reintubation in patients at risk of ARF post extubation; particularly patients with pre-existing cardiac or pulmonary dysfunction.

- NPPV should be applied pre-emptively to patients with a high likelihood of post-extubation ARF; application of NPPV after onset of ARF shows no benefit and may inappropriately delay reintubation.
- Appropriate selection of patients is essential: not all patients would benefit with application of NPPV post extubation.
- *Postoperative ARF*:
  - Cardiothoracic surgery: in thoracic resections, extubation to NPPV has led to a decrease in reintubation rates, shorter length of stay, and improved oxygenation and ventilation. In cardiac surgery, the rate of postoperative pulmonary complications is decreased but there is no significant reduction in reintubation rates. To prevent surgical complications, lower pressure settings are advisable.
  - Abdominal surgery: data show that the postoperative use of NPPV can prevent atelectasis and associated complications (hypoxia, postoperative pneumonia). Decreased reintubation rates are also evident.
- *Patients with a DNR order*:
  - NPPV can be used to relieve dyspnea.
  - Use depends on the goals of care: either for palliation or as the maximal level of respiratory support.
  - HFNC may also be used in palliation and may be better tolerated.
- *NPPV as a bridge to extubation*:
  - In patients with COPD, extubation directly to NPPV may be an option. These patients are often borderline during their spontaneous breathing trials and thus their extubation can often be delayed.
  - Extubating these patients directly to NPPV has been successful, without increased rates of reintubation and with decreased length of mechanical ventilation.
- *NPPV as a preoxygenation modality prior to Intubation*:
  - Patients with ARF are often initially placed on NPPV and subsequently progress to intubation.
  - In these patients, the NPPV device may be used as a preoxygenation tool.
  - The FiO_2 should always be set to 100% when NPPV is used for this indication.
- *NPPV during procedures in patients at risk for respiratory failure*:
  - Patients undergoing bronchoscopy can be at risk for respiratory failure and have increased respiratory demands; the use of NPPV in these patients peri-procedure has been successfully described throughout the literature.
  - Patients undergoing GI endoscopy with a tenuous respiratory status may also benefit from peri-procedure NPPV; however, the data are more scant and the risk of complications, including aspiration, are higher when invasive GI procedures are undertaken on NPPV. Nevertheless, several cases have been described and this may be an option for a patient with contraindications to intubation (such as DNI status).

Predictors of success and failure of NPPV

Predictors of success

- Higher level of consciousness.
- Younger age.
- Lower severity of illness.
- Less severe gas exchange abnormalities.
- Lack of severe acidosis pH 7.10–7.35.
- Minimal air leak around the interface.

Predictors of failure

- *On admission*:
  - Encephalopathy (except AECOPD patients).
  - Low pH (especially <7.1).
  - Older age.
  - Multiple comorbidities.
  - Multiorgan dysfunction.
  - Respiratory arrest.
  - Hemodynamic instability.
  - Patient dyssynchrony with NPPV.

- *On reassessment (0.5–2 hours)*:
  - No improvement in mental state.
  - No improvement in pH/$PaCO_2$.
  - No improvement in respiratory rate or work of breathing.

Guidelines for use

Protocol for initiation of NPPV

- Monitor in ICU or other closely monitored settings, such as step down or respiratory care units.
- Oximetry and vital signs monitoring as clinically indicated, preferably continuous.
- Position patient at >30° angle.
- Select the appropriate interface based on face size and patient comfort.
- Select ventilator and mode of ventilation.
- Avoid excessive strap tension from headgear to prevent discomfort and potential skin ulceration.
- In spontaneously triggered mode with backup rate:
  - Initial settings: IPAP 8–12 cmH_2O, EPAP 3–5 cmH_2O, RR 6–10/min.
  - COPD/asthma: start IPAP 8 cmH_2O, EPAP 4 cmH_2O.
  - Congestive heart failure: start CPAP 8–10 or bilevel 8/4 (if hypercapnic).
- Increase IPAP in increments of 2–4 cmH_2O (up to 10–20 cmH_2O) as tolerated with goals:
  - Alleviation of dyspnea.
  - Decreased respiratory rate.
  - Adjust to deliver V_T 6–8 mL/kg of predicted body weight.
  - Patient–ventilator synchrony.
- Add supplemental oxygen, as needed, to keep SpO_2 >90%.
- Humidification may be necessary for comfort.
- Agitated patients may benefit from mild sedation:
  - Requires a closely monitored setting (i.e. ICU).
  - Persistent or worsening agitation is a sign of failure of the NPPV trial.
- Clinical reassessment every 15 minutes for the first 2 hours, and make adjustments as necessary.
- Evaluate arterial blood gas.
- Consider endotracheal intubation if no improvement or deterioration within 2 hours of NPPV trial.

Protocol for initiation of HFNC

- Begin with FiO_2 100% and flow rate of 50 L/min.
- Titrate FiO_2 down as tolerated, maintaining SpO_2 >90%.
- Clinical reassessment to ensure improvement and comfort.

Managing the patient on NPPV

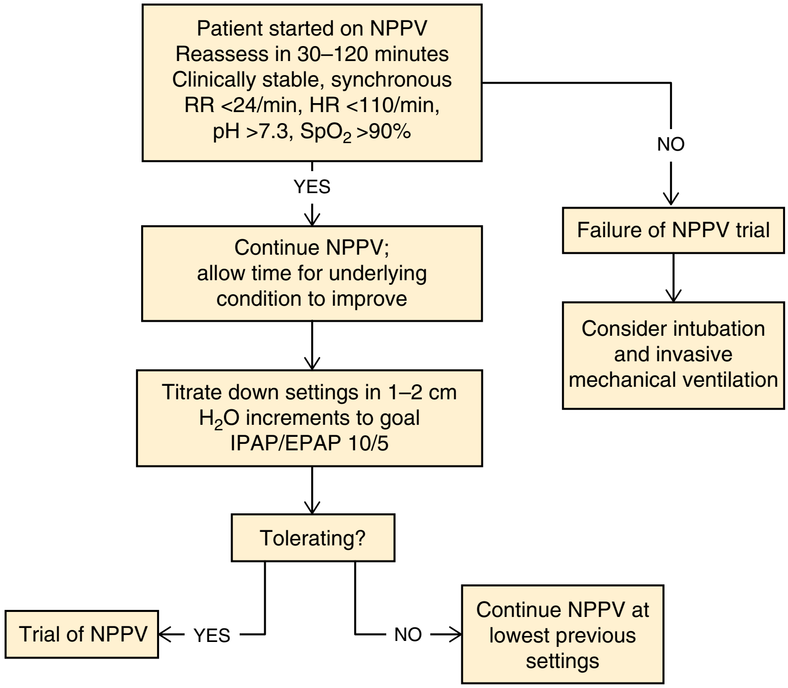
Daily monitoring and weaning

- Daily evaluation for continued need for NPPV. Is condition improved or is patient stabilized?
- If NPPV has been successful in achieving goals, NPPV support may be necessary for only 24–72 hours.
- Currently there is no universally accepted protocol for weaning.
- Algorithm 22.1 outlines an approach to initiation and weaning.

Troubleshooting

- Achieving patient comfort will allow the patient to tolerate NPPV and ultimately may prevent intubation. Intolerance to NPPV is one of the main causes of NPPV failure.
- Use of a ventilator that minimizes leaks, the choice of interface, the humidification system, and appropriate sedation can all improve tolerance.

Algorithm 22.1 Daily evaluation and weaning of NPPV



- Leaks: ensuring good mask fit is integral to the success of NPPV:
  - Poor mask fit may lead to an unacceptably large leak and cause suboptimal ventilation.
  - Masks which leak cannot deliver adequate pressure.
  - Patient discomfort is increased with leak.
  - Using a ventilator with good leak compensation can be helpful. Bilevel ventilators have good leak compensation capabilities.
  - Newer ICU ventilators have NPPV modes which detect leak and automatically adjust.
- Patient dyssynchrony is one of the main limiting factors and is determined by the underlying disease process and the leak.
- Humidification: although the need for humidification is controversial, a dry nasal airway increases resistance and patient discomfort:
  - Humidification is provided by a heated humidifier or moisture exchanger.
  - No significant difference has been found with the use of either method of humidification.
- Sedation: low dose sedation can be considered to control anxiety and improve patient's tolerance of NPPV. A monitored setting is usually required. The following medications can be used:
  - Benzodiazepines (most commonly lorazepam 0.5 mg initial dose).
  - Remifentanil 0.5 μg/kg/min.
  - Dexmedetomidine 0.2 μg/kg/min.
- Claustrophobia: use of a nasal mask may be beneficial in claustrophobic patients.

Complications

- Adverse hemodynamic effects are unusual but have been reported.
- Very low risk of barotrauma.

- Aerophagia:
  - Mild gastric distention, incidence 10–50%.
  - Aspiration of gastric contents, rarely significant at routinely applied levels of inspiratory pressure support.
  - Addition of agents that accelerate intestinal transit (domperidone or simethicone).
  - Decrease in IPAP may be beneficial.
- Airway dryness sinus or ear pain, decreased sputum clearance, or nasal congestion.
- Skin breakdown due to pressure: most common location of skin breakdown is the bridge of the nose:
  - Alternating between different masks helps to prevent skin breakdown.

Reading list

Bersten AD, et al. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. N Engl J Med 1991;325:1825–30.

Keenan SP, et al. Noninvasive positive pressure ventilation in the setting of severe, acute exacerbations of chronic obstructive pulmonary disease: more effective and less expensive. Crit Care Med 2000;28:2094–102.

Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive pressure ventilation for postextubation respiratory distress: a randomized controlled trial. JAMA 2002;287:3238–44.

Lim WJ, et al. NIPPV for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database Syst Rev 2012;12:CD004360.

Meduri GU, et al. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. Chest 1991;100:445–54.

Meduri GU, et al. Noninvasive positive pressure ventilation in status asthmaticus. Chest 1996;110:767–74.

Meeder AM, Tjan DH, van Zanten AR. Noninvasive and invasive positive pressure ventilation for acute respiratory failure in critically ill patients: a comparative cohort study. J Thorac Dis 2016;8(5):813–25.

Mehta S, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med 1997;25:620–8.

Pelosi P, Jaber S. Noninvasive respiratory support in the perioperative period. Curr Opin Anaesthesiol 2010;23:233–8.

Stefan MS, et al. Trends in mechanical ventilation among patients hospitalized with acute exacerbations of COPD in the United States 2001 to 2011. Chest 2015;147(4):959–68.

Xu X, et al. Noninvasive ventilation for acute lung injury a meta-analysis of randomized controlled trials. Heart Lung 2016;45(3):249–57.

Evidence

Type of evidence	Title and comment	Date and reference/weblink
Consensus guideline statement	*International Consensus Conferences in Intensive Care Medicine: Non-invasive Positive Pressure Ventilation in Acute Respiratory Failure. Organized jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Societe de Reanimation de Langue Francaise, 2000* The guidelines establishing general principles of use as adopted by several leading respiratory societies throughout the world. Guidelines are based on analysis of various metadata and review articles	2000 http://www.atsjournals.org/doi/full/10.1164/ajrccm.163.1.ats1000#.Vxvj99KrS70
Consensus guideline statement	*British Thoracic Society/Intensive Care Society Guideline for the ventilatory management of acute hypercapnic respiratory failure in adults*	2002 http://bmjopenrespres.bmj.com/content/3/1/e000133

(*Continued*)

(*Continued*)

Type of evidence	Title and comment	Date and reference/weblink
Meta-analysis	*Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and metaanalysis of randomized controlled trials* Use of NPPV in acute care settings and patient outcomes. The meta analysis data show increased survival rates for patients in whom NPPV was used as primary support therapy and used post extubation	2015 Crit Care Med 2015;43(4):880–8
Review article	*Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting* An analysis of multiple studies and guidelines. Conclusions supported the early use of NPPV in AECOPD, CPE, and to prevent reintubation in these patients	2011 CMAJ 2011;183(3):195–214
RCT	*Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask* The landmark trial of NPPV use and outcomes in patients with AECOPD	1990 N Engl J Med 1990;323:1523–30
RCT	*Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask* The landmark trial of NPPV use and outcomes in patients with cardiogenic pulmonary edema	1991 N Engl J Med 1991;325:1825–30
RCT	*High flow oxygen through nasal cannula in acute hypoxemic respiratory failure* Discusses the benefits of HFNC in patients with acute hypoxemic respiratory failure	2015 N Engl J Med 2015;372:2185–96

Images

Figure 22.1 NPPV nasal–oral mask.

Figure 22.2 High flow nasal cannula.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 23

Acute Respiratory Distress Syndrome

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OVERALL BOTTOM LINE

- ARDS is characterized by non-cardiogenic pulmonary edema, hypoxemia, diffuse alveolar damage, heterogeneous disease distribution, and decreased lung compliance. Diagnosis is made based on the 2012 Berlin definition of ARDS.
- ARDS represents a complex response to local and systemic inflammation as a result of either direct or indirect injury to the lung. It most commonly arises due to underlying sepsis, aspiration of gastric contents, pneumonia, multiple transfusions, or trauma.
- Treatment strategies focus on treating the underlying cause in addition to supportive care while safely maximizing ventilator settings to improve hypoxemia and to decrease ventilator-associated lung injury.
- The ARDS Network study established that a tidal volume of 6 mL/kg of predicted body weight or lower will minimize lung injury and reduce mortality.
- ARDS carries a high mortality. Patients more commonly die from multiple organ failure, superimposed infections, or the underlying conditions that led to ARDS as opposed to hypoxemia itself. The survivors are often left with important functional limitations and decreased quality of life for at least 5 years after their illness.

Background

Definition of disease

- ARDS is a life-threatening clinical syndrome with heterogeneous underlying pathologic processes and is characterized by widespread lung inflammation resulting in bilateral alveolar infiltrates, atelectasis, and hypoxemia.
- The American–European Consensus Conference first established clinical criteria for ARDS in 1994. This was the prevailing definition until the 2012 Berlin definition refined the definition and criteria to improve reliability and predictive validity.

Incidence/prevalence

- The age-adjusted incidence for patients with ARDS is 38.9 per 100 000 person-years.
- There has been a decline in hospital-acquired ARDS with no change in incidence of admissions for ARDS.
- The incidence of lung injury has been shown to increase with age.
- Estimates suggest there are approximately 190 600 new cases annually in the USA.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Table 23.1 Etiologies of ARDS.

Direct	Indirect
Pneumonia Aspiration (gastric contents, near drowning) Lung contusion Inhalation injury (smoke, toxins) Embolism (amniotic, fat, air)	Severe sepsis Shock Trauma Anaphylaxis Non-pulmonary trauma Acute pancreatitis Transfusion-related acute lung injury (TRALI) Massive transfusion Burn injury Drug overdose

Etiology

- ARDS is a clinical syndrome that represents a complex response to local and systemic inflammation with alveolar–capillary injury resulting in non-cardiogenic pulmonary edema, atelectasis, and hypoxemia. The lung injury pathway can be triggered by a variety of primary diseases or processes. Causes can be categorized as direct or indirect pulmonary insults (Table 23.1).
- The most common conditions associated with the onset of ARDS include sepsis, pneumonia, aspiration, and trauma.
- Patients that develop ARDS as a result of a direct pulmonary injury have more severe reductions in lung compliance and may be less responsive to PEEP.

Pathology/pathogenesis

- Regardless of the underlying etiology, an inflammatory response results in neutrophil accumulation in the circulation of the lung.
- The neutrophils are recruited and migrate across the vascular endothelial and alveolar epithelial surfaces and become activated. This increases alveolar–capillary membrane permeability leading to non-cardiogenic pulmonary edema, and atelectasis with a classic pathophysiology of diffuse alveolar damage.
- This change in permeability allows flooding of alveoli and interstitial spaces with pro-inflammatory cytokines (TNF-α, IL-1, IL-8), reactive oxidative species, and protein-rich fluid, resulting in edema and impairing gas exchange.
- High concentrations of protein in the alveoli interfere with the ability of surfactant to keep alveoli open which results in atelectasis.
- The clinical consequences of the ongoing lung injury include impaired oxygenation, decreased lung compliance, and increased pulmonary arterial pressure.
- The progression of ARDS had been thought to evolve through three stages: the exudative phase, fibroproliferative phase, and recovery phase. However, recent evidence suggests that there is significant overlap with less discrete timing and phases.

Exudative phase (0–7 days)

- This phase is characterized by continued accumulation in the alveoli of excessive fluid, protein, and inflammatory cells that have entered the air spaces from the alveolar capillaries.
- Progressive atelectasis decreases the number of alveoli available for ventilation, contributing to worsening hypoxemia.

- Intrapulmonary shunting occurs as more blood passes through the lungs without being oxygenated. This ultimately leads to refractory hypoxemia and low arterial oxygen pressure (PaO_2) that does not improve despite increases in supplemental oxygen therapy (FiO_2).
- Hypoxemia is often the most profound during this phase.

Fibroproliferative phase (7–14 days)

- Some patients achieve complete resolution of lung injury before progressing onto the fibroproliferative stage, whereas others progress directly to fibrosis.
- The balance between pro-inflammatory and anti-inflammatory mediators is thought to be an important determinant of the overall inflammatory response, the extent of lung injury, and clinical outcomes.
- The extent of fibrosis is also related to the severity of the initial injury, ongoing or repetitious lung injury, toxic oxygen effects, and ventilator-associated lung injury.
- Those struggling to recover often enter a fibrotic phase. As the inflammatory response continues, infiltration of fibroblasts leads to collagen deposition, and fibrosis. This results in stiff, poorly compliant lungs.
- The degree of fibrotic changes is quite variable among patients with ARDS. Predominantly fibrotic changes can lead to prolonged ventilator dependency.
- Prolonged ventilator dependency may necessitate tracheostomy and prolonged ventilator weaning. This decision is also based on the extent of other organ function and overall goals of care for each patient.

Recovery phase

- For those patients who instead enter the recovery phase, there is deactivation of anti-inflammatory cytokines produced by neutrophils.
- Deactivated neutrophils undergo apoptosis and phagocytosis. This allows proliferation of type II alveolar cells with squamous metaplasia later resulting in type I alveolar cells, which helps re-establish the epithelial lining of the alveoli.
- This return of structural integrity creates an osmotic gradient, which draws fluid out of the alveoli and promotes resolution of pulmonary edema and atelectasis.
- Oxygenation usually improves to the point of successful liberation from mechanical ventilation.

Predictive/risk factors

There are several diverse conditions associated with the onset of ARDS. Patients with the risk factors listed in Table 23.2 are at increased risk for development of ARDS.

Prevention

BOTTOM LINE

- Given the various diverse etiologies, no one singular intervention has been shown to prevent the development of ARDS.
- Early recognition of at-risk patients and minimizing potential exposures to known risk factors may help prevent or minimize the severity of ARDS.
- Volutrauma and barotrauma from use of large tidal volumes (>6–8 mL/kg of ideal body weight) and excessive fluid administration can predispose at-risk patients to developing ARDS.
- Utilizing a checklist for lung injury prevention incorporates current best practice for ARDS prevention and has been shown to reduce the incidence of ARDS.

Table 23.2 Risk factors for ARDS.

Risk factor	Comments
Sepsis	The inflammatory cascade that results in sepsis may be severe enough to result in lung injury that leads to ARDS
Alcoholism	In the setting of sepsis, alcoholics are at much higher risk due to a predisposition to oxidative lung injury
Trauma	Occurs more commonly in patients with bilateral lung contusions, and fat embolism following long bone fractures
Drug overdose	Most commonly implicated drugs include aspirin, tricyclic antidepressants (TCAs), cocaine, opioids, and phenothiazines
TRALI	Cytokine-mediated process that occurs with any blood product transfusion including fresh frozen plasma, platelets, or packed red blood cells
Massive transfusion	Most commonly in patients requiring transfusion of more than 15 units of red blood cells
Lung transplant	Most at risk during the first week post lung transplant surgery due to primary graft failure. Attributed to imperfect preservation of the lung
Hematopoietic stem cell transplantation	Occurs due to risk of infectious and non-infectious complications

Screening

- There is no standard screening process for ARDS, but early recognition is important.
- Review a patient's history to determine whether a risk or etiology is present, such as timing of a transfusion.
- Check an ABG to determine the degree of hypoxemia based on a patient's PaO_2/FiO_2 ratio.
- Check a chest radiograph.
- Check an echocardiogram to evaluate heart function and to rule out hydrostatic edema.

Primary prevention

- There is no specific therapy to prevent ARDS. Primary prevention is in the form of standard of care treatment for a patient based on their underlying illness.
- In patients who are already on ventilatory support for reasons unrelated to ARDS, low-tidal volume ventilation (6–8 mL/kg PBW), PEEP, and lowest possible FiO_2 have been shown to reduce the risk for ARDS. These interventions prevent alveolar hyperinflation and cyclic stretching which can trigger lung injury.
- A checklist that encompasses other best practice recommendations for lung injury prevention should be used to address other factors that may increase the risk for ARDS. This checklist includes:
  - Aspiration precautions, which includes elevating the head of the bed to 30°, gastric acid neutralization, and oral antiseptic hygiene.
  - Avoidance of excessive fluid administration in patients with shock.
  - Empiric antimicrobial treatment and infection source control based on site of infection and immune status.
  - Limiting blood, platelet, and plasma transfusions unless indicated (i.e. hemoglobin <7 g/dL or if actively bleeding).
  - Re-evaluating non-invasive ventilation use within 30 minutes of initiating it to prevent delay in intubation, if necessary.
  - Utilizing structured handoffs for at-risk patients between providers when transferring patients to ICU.

Diagnosis

BOTTOM LINE

- Taking a detailed history is important to identify a clinical insult.
- Symptoms usually present within 48–72 hours of an inciting event. Physical exam findings are often non-specific and depend on the underlying etiology (i.e. abdominal pain from pancreatitis, physical wounds from trauma).
- Patients are often critically ill, with tachypnea, tachycardia, and hypoxemia. The hypoxemia is often difficult to manage and refractory to supplemental oxygen.
- All patients with suspected ARDS should have imaging, an ABG, and a transthoracic echocardiogram to evaluate for causes of hypoxemia. Beyond this, investigations should be based on the suspected underlying etiology.

Disease definition and severity classification

The Berlin definition of ARDS (2012)	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Based on either CXR or CT scan. Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	200 mmHg < PaO_2/FiO_2 ≤300 mmHg with PEEP or CPAP ≥5 cmH_2O
Moderate	100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP ≥5 cmH_2O
Severe	PaO_2/FiO_2 ≤100 mmHg with PEEP ≥5 cmH_2O

Differential diagnosis

Differential diagnosis	Features
Cardiogenic pulmonary edema	Respiratory crackles, jugular venous distention, peripheral edema, third heart sound
Acute valvular dysfunction	Recent myocardial infarction, history of valvular heart disease, new heart murmur
Pneumonia (typical or atypical)	Productive cough, fever, pleuritic chest pain
Pneumocystis jirovecii pneumonia	Immunocompromised status, respiratory crackles, elevated LDH and β-D-glucan
Acute eosinophilic pneumonia	Fever, cough, diffuse opacities, increased eosinophils on bronchoalveolar lavage
Transfusion-related acute lung injury	Recent transfusion of plasma containing units including fresh frozen plasma, platelets, and packed red blood cells
Acute exacerbation of idiopathic pulmonary fibrosis (IPF) or chronic interstitial lung disease (ILD)	Underlying IPF or ILD with unexplained worsening or development of dyspnea within 30 days with new radiographic infiltrates

Differential diagnosis	Features
Cryptogenic organizing pneumonia	Disease onset in fifth or sixth decade of life. Patients are symptomatic for less than 2 months and have symptoms similar to community-acquired pneumonia
Diffuse alveolar hemorrhage	Often have underlying autoimmune or connective tissue diseases
Acute interstitial pneumonia (Hamman–Rich syndrome)	Affects previously healthy individuals without a prior history of lung disease. Have fever and can sometimes have highly productive cough with thick mucus

Typical presentation

- Initial evaluation of the patient will reveal tachycardia, tachypnea, and hypoxemia. The hypoxemia may be severe enough to warrant intubation and ventilatory support. These findings usually begin within 48–72 hours of the insult.

Clinical diagnosis

History

- A thorough review of a patient's history is essential to determining the cause of ARDS. In many cases the inciting factor may be obvious (e.g. sepsis, trauma, pancreatitis, recent lung transplant).
- Clinicians should specifically ask about a history of cardiac disease or heart failure, chronic lung disease, specifically if there is a history of interstitial lung disease, connective tissue disease, or autoimmune disease, any of which may present similarly.
- Clinicians should also inquire about a history of alcoholism and elicit drug use as these are risk factors that may predispose a patient to ARDS.
- If the patient has been hospitalized prior to evaluation for ARDS the clinician should review the record for factors such as duration of hospitalization (timing and risk for nosocomial infections) as well as receiving blood product transfusion.

Physical examination

- The physical exam will demonstrate a patient in respiratory distress requiring escalating concentrations of supplemental oxygen.
- On auscultation of the lungs, crackles may be heard.
- Further findings will again be determined by the inciting etiology.

Disease severity classification

Severity of ARDS ranges from mild to moderate to severe depending on the patient's PaO_2/FiO_2 ratio (see the Berlin definition of ARDS, 2012).

Laboratory diagnosis

List of diagnostic tests

- There is no specific test to identify ARDS. Laboratory testing is often dictated by the underlying etiology of ARDS.
- Blood tests:
  - Regardless of etiology, an ABG should be obtained to grade the patient's severity of hypoxemia. The measured PaO_2 divided by the FiO_2 is the PaO_2/FiO_2 ratio, which defines the severity of ARDS.
  - For patients with a clinical picture of sepsis, obtaining blood cultures may allow isolation of the pathogen and appropriate antibiotic choices.
- Culture based on suspected site of infection:

- Respiratory culture: if pneumonia or aspiration is suspected as the cause of ARDS, a respiratory culture can help identify the microorganism responsible and appropriate antibiotic administration.
- Urinalysis and urine culture if suspected as a source of sepsis.

List of imaging techniques

- CXR:
  - Used as the initial screening tool for hypoxemic patients. Typical features are bilateral opacities (Figures 23.1 and 23.4).
- CT scan:
  - CXR is often sufficient in evaluating patients for ARDS. CT scans can be performed as an adjunctive test. Chest CT scans have been shown to better characterize the syndrome and often highlight the heterogeneous lung disease distribution (Figures 23.2 and 23.3).
- TTE:
  - A TTE should be used to assess cardiac structure and function to evaluate for heart failure as a cause of pulmonary edema.

Potential pitfalls/common errors made regarding diagnosis of disease

- Patients can suffer from an overlapping ARDS and ARDS mimics (e.g. congestive heart failure).

Treatment

Treatment rationale

- Management of ARDS is focused on optimizing oxygenation, while preventing further lung injury. Less invasive supportive measures like high flow supplemental oxygen or non-invasive ventilation can be attempted if the patient is not rapidly deteriorating and remains closely monitored. Non-invasive measures should never delay intubation when it is necessary (see Algorithm 23.1).
- Most patients require tracheal intubation and mechanical ventilation. Techniques to ensure oxygenation while minimizing barotrauma and oxygen toxicity are critical in these patients.
- Studies with chest CT scans have shown heterogeneous disease distribution with lung areas that have predominately atelectasis or consolidation while other areas are well aerated. These studies are the basis of the ventilatory strategy of lower tidal volumes and avoidance of overdistention of normal lung.
- Treatment strategies that have been shown to improve clinical outcomes are: use of low tidal volume ventilation (6 mL/kg predicted body weight) and use of PEEP (see Table of treatment), avoidance of excessive fluid administration, appropriate sedation to promote ventilator–patient synchrony, paralytics if sedation alone is not adequate, and prone positioning.
- Utilizing a conservative fluid strategy is recommended for ARDS patients. Patients should be maintained with a negative balance once hemodynamic stability has been achieved and is sustained. While there is no difference in 90 day mortality for patients managed with conservative versus liberal fluid strategies, patients have been shown to need 18 hours less mechanical ventilatory support when treated with the conservative fluid strategy.
- Rescue strategies for patients with refractory hypoxemia and difficulty in ventilating with conventional mechanical ventilation strategies include: alternative ventilator modes such as airway pressure release ventilation (APRV) or bi-vent, and veno-venous extracorporeal membrane oxygenation (ECMO). Selected patients with sole pulmonary failure should be considered for referral to an ECMO center. Studies supporting the use of these therapies for mortality reduction are limited and remain controversial.
- Early research suggests that respiratory system compliance (C_{RS}) is strongly related to the volume of aerated functional lung during ARDS (termed functional lung size). A decrease in driving pressure ($\Delta P = V_T/C_{RS}$) is an index that is more strongly associated with survival than V_T or PEEP in patients who are not actively breathing (V_T is normalized to functional lung size instead of predicted body weight).

- Driving pressure can be calculated at the bedside as P_{plat} – PEEP. Driving pressures exceeding 14–18 cmH_2O have been associated with increased mortality in ARDS.
- Interventions that have not shown a survival benefit include: corticosteroids in late ARDS, inhaled nitric oxide, low frequency ventilation, and inhaled synthetic surfactant.

Table of treatment

<table>
<tr><th>Treatment</th><th colspan="15">Comments</th></tr>
<tr><td rowspan="3">HFNC</td><td colspan="15">If ARDS is suspected or confirmed, a trial of HFNC can be utilized to improve hypoxemia in selected patients</td></tr>
<tr><td colspan="15">HFNC provides compressed oxygen and air that has been humidified at higher flow rates. With HFNC, a higher FiO_2 can be delivered at flow rates up to 50 L/min</td></tr>
<tr><td colspan="15">Better tolerated than NPPV since it is delivered through nasal prongs and does not cover the oral airway. Also associated with improved 90 day mortality when compared with NPPV</td></tr>
<tr><td colspan="16"></td></tr>
<tr><td rowspan="2">NPPV</td><td colspan="15">Delivered through a facemask that provides positive pressure to recruit atelectatic alveoli and forces excess fluid to leave the interstitial tissue surrounding the alveoli, allowing better exchange of gases</td></tr>
<tr><td colspan="15">Avoid use in patients with altered mental status, patients who are vomiting, those with an upper gastrointestinal hemorrhage, and patients at risk for aspiration</td></tr>
<tr><td colspan="16"></td></tr>
<tr><td rowspan="6">Invasive mechanical ventilation</td><td colspan="15">Low tidal volume set at 6 mL/kg (or lower) based on PBW (PBW is height based) with goal of maintaining inspiratory plateau pressure <30 cmH_2O is associated with less barotrauma and improved mortality</td></tr>
<tr><td colspan="15">Hypercapnia is often a consequence of low tidal volume ventilation and this is acceptable. The respiratory rate can be increased to a maximum rate of 35 breaths/min. If this is not possible then bicarbonate can be administered. A patient's pH should be maintained above 7.20</td></tr>
<tr><td colspan="15">FiO_2 should be initiated at 100% and titrated down within 24–48 hours to maintain a goal SaO_2 >88%. Prolonged exposure to FiO_2 >60% is associated with oxygen toxicity</td></tr>
<tr><td colspan="15">Achieving FiO_2 <65% may require moderate to high levels of PEEP, although based on severity of disease this may not always be achievable. Use of the ARDSnet PEEP/FiO_2 table can guide therapy:</td></tr>
<tr><td>FiO_2</td><td>0.3</td><td>0.4</td><td>0.4</td><td>0.5</td><td>0.5</td><td>0.6</td><td>0.7</td><td>0.7</td><td>0.7</td><td>0.8</td><td>0.9</td><td>0.9</td><td>0.9</td><td>1.0</td></tr>
<tr><td>PEEP</td><td>5</td><td>5</td><td>8</td><td>8</td><td>10</td><td>10</td><td>10</td><td>12</td><td>14</td><td>14</td><td>14</td><td>16</td><td>18</td><td>18–24</td></tr>
<tr><td colspan="16"></td></tr>
<tr><td>Sedatives</td><td colspan="15">Use of sedatives should be geared to ensuring patient–ventilator synchrony and to prevent patient agitation, which may lead to mechanical ventilation-associated acute lung injury</td></tr>
<tr><td colspan="16"></td></tr>
<tr><td rowspan="3">Neuromuscular-blocking agents</td><td colspan="15">Utilize within 48 hours of onset of severe ARDS (P:F ratio <150 and PEEP ≥5 cmH_2O) to promote ventilator synchrony if sedatives are not sufficient</td></tr>
<tr><td colspan="15">Paralytics must always be used in conjunction with sedatives</td></tr>
<tr><td colspan="15">Limit use to prevent development of critical illness polyneuropathy</td></tr>
</table>

(*Continued*)

Treatment	Comments
Prone positioning	Utilize within 36 hours of onset of severe ARDS (P:F ≤150 and PEEP >5 cmH_2O)
	Patients are placed in the prone position for at least 16 hours per day
	ABG for the PaO_2/FiO_2 ratio should be taken just before prone positioning, 1 hour after, just before returning to supine position, and again 4 hours after
	Goal arterial pH of 7.20–7.45
	Can be used daily up to 28 days
	Prone positioning should be considered in institutions with trained staff and equipment. Prone positioning may place patients at risk for accidental extubation, dislodged IV catheters, skin ulcerations, and corneal abrasions if the patient is not appropriately prepared
Nutrition	Nutritional support is recommended in patients who are expected to require mechanical ventilation for 48–72 hours
	Enteral nutrition is favored over parenteral nutrition
Prophylaxis	Deep vein thrombosis prophylaxis is indicated using subcutaneous unfractionated heparin, subcutaneous enoxaparin or subcutaneous fondaparinux unless there is a specific contraindication
	Stress ulcer prophylaxis using H_2-blockers or proton pump inhibitors is indicated for patients mechanically ventilated for more than 48 hours to reduce the risk of stress ulcer bleeding

Prevention/management of complications

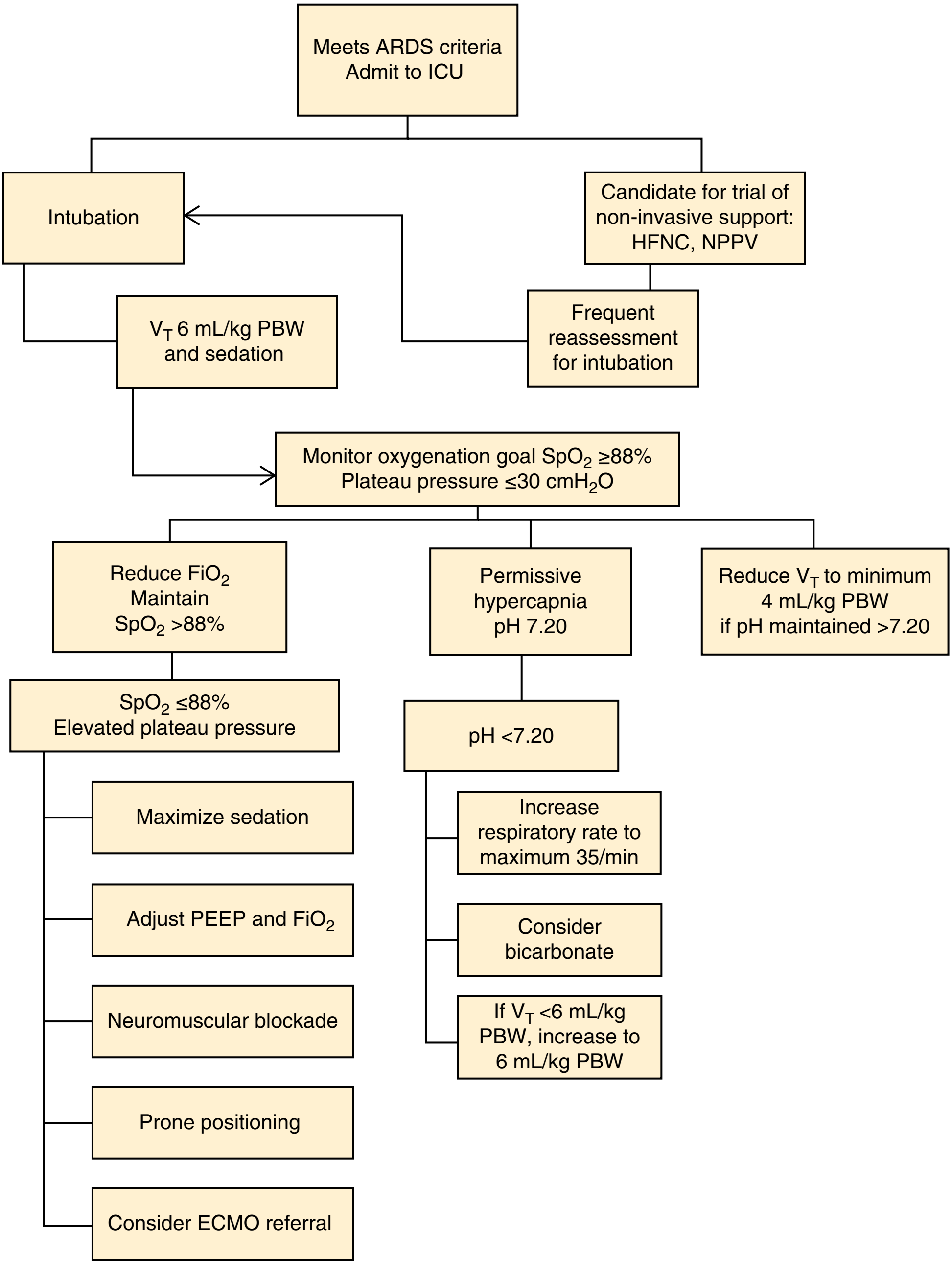
- Mechanically ventilated patients are at an increased risk for barotrauma (e.g. pneumothorax). If a patient acutely develops worsening hypoxemia or hemodynamic instability, auscultation of the lungs, chest radiography, and chest ultrasound (in institutions with appropriate ultrasound expertise) are indicated to rule out this potential complication. If present, an emergent chest tube should be placed.
- Daily chest radiographs may be performed to assess for disease progression, location of the endotracheal tube, and for potential complications of barotrauma.
- Caution should be used in patients receiving neuromuscular-blocking agents. These patients are at risk for death should they inadvertently become disconnected from the ventilator. Ensure alarms are set to alert medical staff of any possible malfunction.

CLINICAL PEARLS

- The majority of patients who develop ARDS will require invasive mechanical ventilation.
- Low tidal volume (6 mL/kg of PBW) ventilation has been shown to reduce overall mortality.
- Early use of neuromuscular blockade and prone positioning (at least 16 hours per day) in severe ARDS has been shown to reduce overall mortality.
- Other 'rescue' strategies in severe ARDS may be considered for selected patients but current evidence does not support their routine use.

Management/treatment algorithm (Algorithm 23.1)

Algorithm 23.1 **ARDS management/treatment algorithm**



Special populations

Pregnancy

- ARDS in pregnancy may be due to previously described conditions and risk factors, or due to pregnancy-related conditions. These include, but are not limited to, amniotic fluid embolism, chorioamnionitis, and severe pyelonephritis. Limited research exists on the management of ARDS in pregnancy, and treatment approaches are similar to those for non-pregnant patients.
- A multidisciplinary approach involving maternal–fetal medicine, neonatology, and intensivists is recommended to optimize maternal and fetal outcomes.

Elderly

The management of ARDS in the elderly is the same as in other adult patients.

Prognosis

BOTTOM LINE

- Overall mortality is estimated to be 40%. Older patients appear to be at an increased risk for death.
- Early deaths are generally due to the underlying condition of ARDS, whereas later deaths may be due to hospital-acquired events such as secondary infection.
- No single risk factor has been proven to be superior in predicting mortality.
- Survivors commonly face significant morbidity from cognitive, psychological and physical deficits leading to a poorer quality of life.

Prognosis for treated patients

- Survival has improved over time, which may be attributable to better supportive care and improved ventilatory strategies, such as low tidal volume ventilation.
- Patients 15–19 years of age have a mortality rate of 24%, while the mortality rate is 60% in patients aged 85 years and older.
- ARDS survivors may suffer from exercise limitations, as well as other physical and psychological sequelae that persist to up to 5 years after resolution of ARDS.
- The persistent health burden of the critical illness is the equivalent of a chronic disease with similar health care utilization.
- Family caregivers of ARDS survivors have been found to suffer from psychological and emotional dysfunction that persists up to 5 years after resolution of ARDS in their family member.

Follow-up tests and monitoring

- After recovery from ARDS, there is no standard follow-up. However, patients may benefit from follow-up if they experience signs and symptoms of functional impairment (e.g. impaired pulmonary function).
- Close monitoring by a clinician and aggressive rehabilitation are cornerstones of care.
- Psychological support from a licensed professional can be beneficial, if necessary.

Reading list

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Guidelines

International society guidelines

Title	Source	Date and weblink
Framework and fund of knowledge for ARDS research	NIH-NHLBI ARDS Network	2016 http://www.ardsnet.org/

Evidence

Type of evidence	Title and comment	Date and reference/weblink
Ten randomized controlled trials and one observational study	*The NIH-NHLBI ARDS Network was a research network formed to study treatment of acute respiratory distress syndrome* Network investigators reported improved survival with lung protective ventilation and shortened duration of mechanical ventilation with conservative fluid management. Additional trials informed best practices by suggesting no role for routine use of corticosteroids, beta-agonists, pulmonary artery catheterization, or early full calorie enteral nutrition	2016 http://www.ardsnet.org/
Meta-analysis	*Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury* Available evidence from a limited number of RCTs shows better outcomes with routine use of low tidal volume, but not high PEEP ventilation in unselected patients with ARDS or acute lung injury	2009 Ann Intern Med 2009;151:566
RCT	*Prone positioning in severe acute respiratory distress syndrome* In patients with severe ARDS, early application of prolonged prone positioning sessions significantly decreased 28 and 90 day mortality	2013 N Engl J Med 2013;368:2159

Images

Figures 23.1–23.4 are radiographic images typical of a patient with ARDS. These images highlight one patient's course through hospital, with tracheostomy ultimately necessary for continued ventilator weaning.

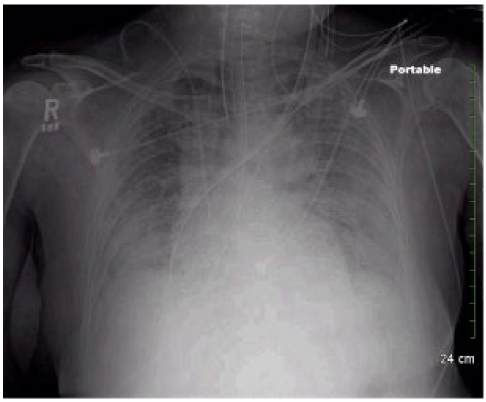

Figure 23.1 Chest radiograph of a patient in respiratory distress secondary to ARDS requiring endotracheal intubation.

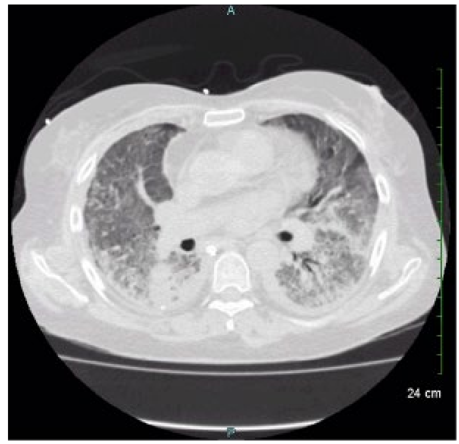

Figure 23.2 Admission CT chest of a patient with ARDS due to aspiration pneumonia.

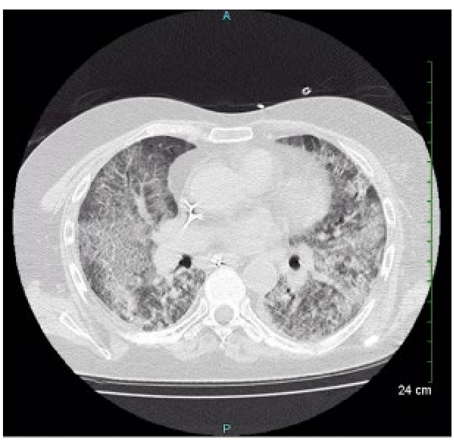

Figure 23.3 CT chest of a patient with ARDS mid-hospitalization showing diffuse lung disease manifested as predominantly groundglass and interlobular/intralobular septal thickening.

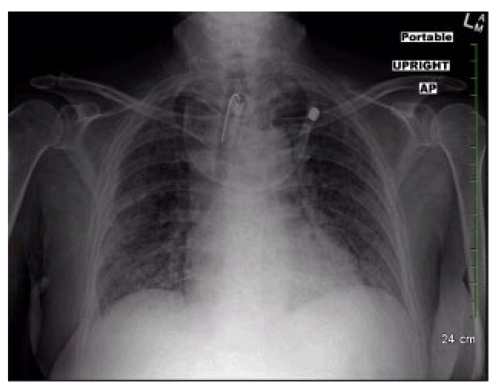

Figure 23.4 CXR of the patient prior to discharge from the hospital. Bilateral hazy and reticular opacities representing ARDS persisted 3 weeks after admission.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 24

Bronchospasm and Chronic Obstructive Pulmonary Disease

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OVERALL BOTTOM LINE

- Acute severe asthma (status asthmaticus) and severe acute exacerbation of COPD (AECOPD) are life-threatening conditions requiring the ICU.
- Successful patient outcomes depend on risk stratification, early diagnosis, early recognition of impending respiratory failure, and appropriate application of mechanical ventilatory support.
- The primary medications are inhaled bronchodilators and systemic corticosteroids.
- The principles of ventilator management in bronchospastic diseases are to support the patient's respirations, allow time for exhalation, and minimize dynamic hyperinflation and its consequences of barotrauma and cardiovascular collapse.
- With appropriate and aggressive management, patients may be discharged from the ICU and return to baseline functional status.

Background

Definition of disease

- The Global Initiative for Asthma (GINA) defines asthma as a 'common, chronic, heterogeneous respiratory disease characterized by variable airflow limitation and usually associated with airway hyper-responsiveness and chronic airway inflammation.'
- The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) defines COPD as a 'common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.'

Disease classification

- Acute severe asthma (status asthmaticus) is an acute, severe asthma exacerbation that does not respond to initial intensive medical therapy. Patients with acute severe asthma often require ventilatory assistance.
- Acute exacerbation of COPD (AECOPD) is a clinical diagnosis characterized by acute worsening of a patient's respiratory symptoms, including increased cough, sputum production, and/or dyspnea. Severe AECOPD may progress to acute respiratory failure requiring ventilatory assistance.

Incidence/prevalence

- More than 25 million people in the USA suffer from asthma. Acute asthma exacerbations account for 1–2 million emergency department visits annually: 25% of these patients require hospitalization; 5–10% of hospitalized patients require ICU admission. In-hospital asthma mortality is approximately 0.5%.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- In the USA, moderate to severe COPD affects more than 65 million people and is the third leading cause of death. COPD is a comorbid condition in nearly 9% of all patients admitted to the ICU and independently contributes to ICU mortality. Severe AECOPD accounts for approximately 2.5% of ICU admissions for acute respiratory failure and carries an estimated in-hospital mortality rate of 5–20%.
- The global prevalence of asthma and COPD is increasing. Important associated factors are socioeconomic status, smoking behaviors, and exposure to outdoor, indoor, and occupational air pollution.

Etiology

- The most common causes of acute severe asthma and AECOPD requiring ICU admission are bacterial and viral respiratory tract infections.
- Bacterial pathogens are mainly implicated in AECOPD, whereas viral infections are most often associated with acute severe asthma.
- In asthmatics, significant exposure to extrinsic allergens, food allergens, or NSAIDs may also trigger sudden exacerbations.
- In patients with COPD, undiagnosed venous thromboembolism, decompensated heart failure, and natural progression of disease may contribute to AECOPD.
- Additional causes of exacerbation include inadequate baseline control, medication non-compliance, inhalation of recreational drugs, and exposure to air pollutants.

Pathology/pathogenesis

- Airway inflammation and airway wall edema are present in both asthma and COPD.
  - Inflammation in asthma is triggered by allergic bronchial hyper-responsiveness to inhaled allergens. The inflammatory response is driven by airway infiltration by eosinophils, neutrophils, stimulated Th2 lymphocytes, and activated mast cells. Cytokine-mediated airway injury ensues via the release of interleukins (particularly IL-4, IL-5), GM-CSF, allergen-specific IgE, and leukotrienes.
  - Inflammatory cells trigger a cytokine cascade that results in bronchoconstriction via smooth muscle contraction, mucous gland secretion, and further airway inflammation.
  - Airway inflammation in COPD results from inhalation of noxious particles and gases – predominantly cigarette smoke. It is chronic in nature and is characterized by neutrophil-predominant inflammatory cells with increased mucous production. Continued lung parenchymal destruction leads to emphysema and impaired gas exchange.
- Airflow obstruction is the pathophysiologic hallmark of both severe acute asthma and severe AECOPD. Narrowing of the airways leads to airflow limitation and increased airway resistance.
  - In asthma, airflow obstruction results from a combination of airway inflammation and edema, airway smooth muscle contraction, mucus plugging of the airways, and airway remodeling. Both inspiratory and expiratory flow rates are limited.
  - In COPD with emphysema, airflow limitation is most pronounced during expiration. Parenchymal destruction leads to a loss of airway tethering with intrapulmonary airway collapse during expiration.
- Dynamic hyperinflation:
  - Tachypnea in the setting of airflow limitation results in incomplete exhalation and hyperinflation. This leads to the increases in end-expiratory lung volumes and alveolar pressures referred to as intrinsic PEEP or auto-PEEP.
  - In an effort to completely exhale each breath, expiratory muscles are recruited with an increase in pleural pressures. This is often insufficient to overcome severe airways obstruction and hyperinflation worsens with each breath.
  - Hyperinflation also results in diaphragm flattening and inefficient expiratory muscle contraction, further worsening expiratory flow and dynamic hyperinflation.

- In patients with severe AECOPD, increased pleural pressures will cause airway collapse and progressive hyperinflation.
- Consequences of persistent and progressive airways obstruction:
  - Increased dead space ventilation results in severe ventilation–perfusion (V/Q) mismatch and hypoxemia.
  - Alveolar overdistension introduces high risk for barotrauma with ventilatory and hemodynamic compromise.
  - Air trapping increases intrathoracic pressure, which impedes systemic venous return. Decreases in right ventricular preload and stroke volume cause hypotension and may lead to shock.
  - The high work of breathing cannot be sustained. A combination of increased metabolic demands of the respiratory muscles, hypoxemia, and hypoperfusion worsens hypercapnia and results in respiratory failure.
  - Persistent hypoxemia may have additional harmful effects including neurologic damage, cardiac arrhythmia, and cardiac ischemia.

Predictive/risk factors

- Patients requiring mechanical ventilation for either acute severe asthma or severe AECOPD are at high risk for death.
- Secondary complications from severe airways obstruction and/or mechanical ventilation include hemodynamic instability from dynamic hyperinflation, barotrauma, and severe acidemia.
- Additional risk factors are listed in Table 24.1.

Table 24.1 Additional risk factors for asthma and COPD-related deaths.

Asthma-related death	COPD-related death
A history of near-fatal asthma requiring mechanical ventilation or ICU admission	Older age
Hospitalization or emergency care visit for asthma in the past year	Male sex
Current or recent use of oral corticosteroids	Low body mass index
Not currently using inhaled corticosteroids	Cardiac failure
Overuse of short-acting β_2-agonist (more than one canister/month)	Chronic renal failure
Difficulty perceiving asthma symptoms or severity of exacerbations	Long-term oxygen therapy
Major psychological or socioeconomic problems	GOLD stage 4 COPD
Poor adherence with asthma medications	Cor pulmonale
Illicit drug use	Elevated troponin level
Cardiovascular comorbidities or chronic lung disease	Confusion

Prevention

CLINICAL PEARLS

- Prevention of smoking initiation is critical to prevent the development of COPD.
- Smoking cessation and avoidance of inhalational allergens/triggers may prevent COPD and asthma exacerbations.
- Influenza and pneumococcal vaccinations are important measures to prevent acute severe asthma exacerbation and AECOPD.

Primary prevention

- COPD is largely a preventable disease, as more than 75% of cases are attributed to cigarette smoking.

Secondary prevention

- Early detection and appropriate management of disease is crucial to prevent progression and complications of asthma and COPD.
- All active smokers should be enrolled in a smoking cessation program.
- Patients should be educated on the avoidance of known allergen/inhalational triggers.
- Influenza and pneumococcal vaccinations are recommended for all patients with asthma and COPD.

Diagnosis

CLINICAL PEARLS

- Severe respiratory symptoms refractory to increased use of rescue medications can indicate acute severe asthma or AECOPD.
- History-taking should address risk stratification for severe exacerbation and respiratory failure.
- Physical examination can reveal impending respiratory failure and hemodynamic compromise.

Differential diagnosis

Differential diagnosis	Features
Upper airway obstruction	Orofacial swelling, drooling, dysphonia, stridor
Airway foreign body aspiration/ endobronchial lesion	Chronic cough, localized wheeze, fever, hemoptysis, purulent sputum
Acute bronchitis/pneumonia	Fever, productive cough, rales/rhonchi
Bronchiectasis with exacerbation	Fever, recurrent infections, productive cough, hemoptysis
Tracheobronchomalacia	Cough, sputum retention, recurrent infections, airway collapse and air trapping on dynamic CT chest
Pulmonary embolism	Pleuritic chest pain, symptoms of deep vein thrombosis, filling defect on chest CT angiography
Congestive heart failure exacerbation	Orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema, rales, evidence of volume overload, pulmonary edema on chest radiograph, elevated BNP
Myocardial infarction	Angina pectoris, ECG consistent with myocardial ischemia, elevated cardiac biomarkers
Paradoxical vocal fold motion	Recurrent wheezing, stridor, abnormal vocal cord adduction on direct laryngoscopy
Hyperventilation syndrome	Intermittent hyperventilation with spontaneous resolution, sense of fear or anxiety, parasthesias

Typical presentation

- Patients with acute severe asthma present with severe dyspnea even at rest, wheezing, difficulty speaking and chest tightness. Patients may have had recent exposure to known or unknown triggers. Patients typically report worsening symptoms despite increased use of short-acting β_2-agonist therapy.

- Patients with severe AECOPD present with progression of their baseline symptoms including worsening dyspnea, cough, wheezing, and exercise intolerance. They may report discoloration and increased volume of sputum. Overt hemoptysis is rare, but streaks or flecks of blood in the sputum are not uncommon.

Clinical diagnosis

History

- Presence of constitutional symptoms.
- Presence of respiratory symptoms including dyspnea, cough, wheezing, hemoptysis, sputum production (volume, color, change from baseline), pleuritic or exertional chest pain, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema.
- Onset, duration, frequency, and timing of symptoms.
- Symptoms include sleep disturbance, exercise intolerance, or limitation in activities of daily living.
- Alleviating and exacerbating factors.
- Exposure to sick contacts, significant allergens at home or work.
- Prior history of exacerbations, use of oral corticosteroids, emergency care or hospitalizations.
- Prior intubation or ICU admission.
- Adherence to medication regimen, frequency of rescue medication use, recent changes in medication regimen.

Physical examination

- Document vital signs including temperature, blood pressure, heart rate, respiratory rate, and continuous pulse oximetry. Pulsus paradoxus indicates severe airflow obstruction.
- Examine the patient's general appearance. Agitation, anxiety, upright or forward-leaning position indicates severe disease.
- Assess for signs of impending respiratory failure including cyanosis, nasal flaring, suprasternal retractions, accessory muscle use, paradoxical breathing (abnormal or dysynchronous movement of the chest wall and/or abdomen during respiration), and the inability to complete full sentences. Ominous signs include confusion or somnolence, 'silent chest,' hypotension, and bradycardia.
- Inspect the oral airway to prepare for potential intubation.
- Auscultate the lungs to identify inspiratory and/or expiratory wheezing, diminished breath sounds, or other sounds that may support an alternate diagnosis.
- Listen for stridor.
- Auscultate the heart for brady- or tachyarrhythmias. Note the presence of jugular venous distension, hepatojugular reflex, and lower extremity edema.
- Identify clubbing of the extremities.
- Evaluate for signs of barotrauma including absent breath sounds, jugular venous distension, subcutaneous emphysema, and deviated sternal notch.
- In the ventilated patient, serial examinations should assess for barotrauma and the development of auto-PEEP:
  - Auscultate for bilateral, symmetric breath sounds.
  - Palpate the neck and chest wall for subcutaneous emphysema.
  - Listen carefully to the expiratory phase; if the next ventilator breath interrupts complete exhalation, the patient is likely developing auto-PEEP.

Laboratory diagnosis

List of diagnostic tests

- Arterial blood gas should be routinely ordered for patients with acute severe asthma or severe AECOPD.

- AECOPD may present with acute or acute-on-chronic CO_2 retention. An elevated bicarbonate level may be a clue to chronic hypercapnia in an individual with known severe COPD. Hypoxemia may also be present, but use of chronic supplemental oxygen should be considered in the interpretation.
- Acute severe asthma often presents with hypoxemia and hypocapnia. Normocapnia or mild hypercapnia may indicate impending respiratory failure.

- CBC should be ordered in all patients with AECOPD and status asthmaticus.
- Serum electrolytes (potassium, magnesium, phosphate) should be monitored in patients using frequent β_2-agonist therapy.
- ECG should be routinely ordered to evaluate for myocardial ischemia, arrhythmia, and right ventricular strain pattern.
- Consider obtaining cardiac biomarkers (troponin-T, BNP) in patients with AECOPD or with presentation concerning for myocardial ischemia, left-sided heart failure, or cor pulmonale.
- Obtain theophylline level for asthmatics taking this medication.
- Influenza/viral culture and/or bacterial sputum culture should be obtained in patients with relevant symptoms of infection.

List of imaging techniques

- Chest radiograph: evaluate for consolidation, barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema (Figure 24.1)), and pulmonary edema.
- CT angiography: consider when presentation is suspicious for acute pulmonary embolism. Increased index of suspicion is recommended in AECOPD patients without a clear precipitating factor.
- Serial peak expiratory flow (PEF) monitoring is recommended for patients with asthma who are able to participate in testing. A decrease in PEF to less than 40% predicted or personal best indicates a severe exacerbation. Improvements in PEF indicate a response to therapy.
- In centers with appropriate ultrasound expertise, point-of-care chest ultrasonography may be used to detect pneumothorax in mechanically ventilated patients with acute severe asthma or AECOPD.

Potential pitfalls/common errors made regarding diagnosis of disease

- Incomplete history of prior exacerbations or respiratory failure that may inform risk stratification.
- Failure to maintain a broad differential diagnosis.
- Delayed recognition of impending respiratory failure, particularly in acute severe asthma.

Treatment

Treatment rationale

- Immediate assessment and treatment of compromised respiratory and hemodynamic status is critical to preventing and managing respiratory failure and cardiovascular collapse.
- Invasive and non-invasive positive pressure ventilation are life-saving therapies for patients with acute respiratory failure from obstructive airways processes. Careful patient selection (for invasive versus non-invasive ventilation strategies) and appropriate monitoring is critical.
- First line pharmacologic therapy for both acute severe asthma and AECOPD is the administration of bronchodilators and corticosteroids.
- Antibiotics should be administered in patients with signs and symptoms of infection.
- Adjunctive therapies to mechanical ventilation including deep sedation, neuromuscular blockade, anesthetic agents (intravenous ketamine, inhaled anesthetics), ECMO, and $ECCO_2R$ (extracorporeal CO_2 removal) should be considered for refractory cases.

When to hospitalize

- Indicators of need for hospitalization in AECOPD:
  - Older age.
  - Severe underlying COPD.
  - Use of long-term oxygen therapy.
  - Difficulty managing disease at home.
  - Significant cardiac comorbidities.
  - Failure to respond to initial medical treatment.
  - Signs of overt or impending respiratory failure.
- Indicators of need for hospitalization in acute asthma exacerbation:
  - Severe underlying asthma.
  - Failure to respond to initial medical treatment.
  - Post-treatment improvement in PEF remains less than 40% predicted or personal best.
  - ICU admission for overt or impending respiratory failure, respiratory arrest, impaired consciousness, or refractory hypoxemia or hypercarbia.

Managing the hospitalized patient

Overview of management for acute severe asthma or AECOPD

Oxygen supplementation	Target saturation 88–92% Excessive oxygen may have deleterious effects in AECOPD
Non-invasive positive pressure ventilation	First line therapy in carefully selected patients with respiratory failure from AECOPD
Mechanical ventilation	Target low respiratory rate to allow prolonged expiratory time Maintain plateau pressures <30 cmH_2O Monitor for auto-PEEP
Inhaled bronchodilators	Administer every 20 minutes to every hour Continuous delivery may be required
Systemic corticosteroids	Administer equivalent of methylprednisolone 60–125 mg IV every 6 hours Taper with clinical improvement
Antibiotics	Initiate antibiotic treatments in patients with evidence of infection
Sedation	Target ventilator synchrony
Neuromuscular blockade	Administer for ventilator asynchrony, severe auto-PEEP, and poorly controlled airway pressures
ECMO and $ECCO_2R$	Consider expert consultation in patients on maximal therapy with refractory hypoxemia, hypercapnia, or hemodynamic compromise
Anesthetic agents	Consider expert consultation in patients on maximal therapy with refractory acidosis, life-threatening auto-PEEP, and poorly controlled airway pressures

Supplemental oxygen

- Target saturation in acute severe asthma and severe AECOPD is 88–92%.
- Excessive oxygen supplementation may have deleterious effects in AECOPD patients including progressive hypercapnia from V/Q mismatch, decreased binding of carbon dioxide to hemoglobin due to the Haldane effect, and blunted ventilatory drive.

Non-invasive positive pressure ventilation (NPPV)

- NPPV is increasingly being used as first line ventilatory support in patients with severe AECOPD.
- Positive expiratory pressure leads to airway dilation, improves ventilation, and improves gas exchange. Positive inspiratory pressure alleviates the work of inspiratory muscles and relieves dyspnea.
- In AECOPD, the use of NPPV can prevent intubation, shorten length of stay, and significantly reduce mortality (NNT = 4). This mortality reduction is largely attributed to the avoidance of invasive mechanical ventilation-associated complications.
- Patients on NPPV must be monitored closely. Improvement in respiratory acidosis, work of breathing, and confusion should be observed within 1–2 hours of initiation. If no improvement or decline, rapidly move to invasive mechanical ventilation.
- The use of NPPV for acute asthma exacerbation remains controversial. NPPV may be used in selected asthmatics with caution and vigilance in monitoring.

Indications for NPPV in AECOPD

- Respiratory acidosis.
- Evidence of respiratory muscle fatigue.
- Use of accessory muscles, paradoxical respiratory pattern.

Contraindications to NPPV

- Cardiopulmonary arrest.
- Hemodynamic instability.
- Altered mental status (excluding hypercapnic encephalopathy).
- Inability to protect the airway.
- Active emesis, hematemesis, copious oral secretions.
- Insufficient mask fit.

Initial settings for NPPV

- Start inspiratory pressure IPAP = 8 cmH_2O, expiratory pressure EPAP = 4 cmH_2O.
- Increase IPAP in increments of 2–4 cmH_2O (up to 10–20 cmH_2O) as tolerated, with goals:
  - Alleviation of dyspnea.
  - Decreased respiratory rate.
  - Adjust to deliver V_T 6–8 mL/kg predicted body weight.
  - Patient–ventilator synchrony.

Invasive mechanical ventilation (IMV)

- The aim of IMV is to assume the work of breathing and maintain gas exchange while avoiding the complications of dynamic hyperinflation.
- Early intubation is advised for patients who do not respond to aggressive treatment, deteriorate despite aggressive treatment, or show signs of impending respiratory failure.

Indications for IMV

- Respiratory or cardiac arrest.
- Inability to tolerate NPPV or NPPV failure.
- Hemodynamic instability.
- Inability to clear secretions.
- Persistent diminished consciousness or agitation.
- Refractory hypercapnia or hypoxemia.

Intubation

- Physicians experienced with difficult airway management should perform intubation in a controlled setting.

- Anticipate and prepare for post-intubation hemodynamic instability. Venous return is impaired by the presence of dynamic hyperinflation and worsened with positive pressure ventilation. Intravenous fluid resuscitation and vasopressors may be required.

Ventilator settings

- Controlled modes of ventilation – either pressure controlled or volume controlled – are recommended.
- Initial settings for volume-controlled ventilation should target a low tidal volume 6–8 mL/kg predicted body weight, respiratory rate of 10–12 breaths/min, and FiO_2 of 100%. Respiratory rate is set low in order to prolong expiratory time and allow expiratory flow to reach zero before the next inhalation (Figure 24.2).
- Initial PEEP setting of 0–5 cmH_2O is recommended in patients with acute severe asthma or severe AECOPD.
- Intrinsic PEEP should be measured using an expiratory hold maneuver (Figure 24.3). However, caution must be exercised to not underestimate auto-PEEP in patients with severe airways obstruction. With severe bronchospasm, airways that are not in communication with main airways may be obstructed due to edema and mucous and, although overdistended, not measured as auto-PEEP. If a patient has hemodynamic signs consistent with auto-PEEP and clinical examination showing continued expiration when the next ventilator breath is given, assume there is significant auto-PEEP.
- Significant auto-PEEP must be treated. This may be achieved with improved patient–ventilator synchrony, reduced inspiratory to expiratory time ratio, and continued medical treatment of bronchoconstriction.
- Extrinsic PEEP can be added for patients with severe air trapping who are allowed spontaneous breaths. This may reduce work of breathing to trigger inspiration, but may also result in worsened air trapping and dangerously high inspiratory pressure if not performed under expert supervision and monitoring.
- Plateau pressures should be monitored closely and maintained below 30 cmH_2O. Peak pressures should be maintained as low as possible.
- For pressure-controlled ventilation, ensure that adequate tidal volumes are achieved.
- Permissive hypercapnia refers to permitting a $PaCO_2$ of 60–80 mmHg and pH as low as 7.2. Elevated $PaCO_2$ is the result of reducing minute ventilation, allowing prolonged time for exhalation in order to reduce auto-PEEP. Permissive hypercapnia is typically necessary in acute severe asthma to allow auto-PEEP reduction strategies. Permissive hypercapnia is problematic for patients with increased intracranial pressure, severe coronary disease, or severe metabolic acidosis.
- Deep sedation is typically required to ensure patient–ventilator synchrony and to reduce risk of barotrauma.
- Neuromuscular blockade may be required in severe cases.

Sedation for IMV

- Continuous sedative infusion is a mainstay of therapy, particularly for mechanically ventilated patients with status asthmaticus.
- A validated sedation scale, such as the Richmond Agitation-Sedation Scale (RASS), should be utilized. Until airflow limitation state has improved, patients with acute severe asthma or severe AECOPD typically require moderate to deep sedation (often RASS –3 to –4) to achieve comfort and ventilator synchrony.
- Propofol by continuous infusion is commonly used and may have additional bronchodilator effects.
- Additional opiate and/or benzodiazepine infusions may be required to achieve desired level of sedation and ventilator synchrony. Morphine is associated with histamine release but this seems to have minimal clinical importance. Fentanyl is not associated with histamine release.
- Despite deep sedation, patients with persistent ventilator asynchrony or progressive dynamic hyperinflation may require neuromuscular blockade. Cisatracurium loading dose followed by continuous infusion is frequently used.

Adjunctive therapies

- Bronchoscopy may be rarely required for airway clearance in intubated patients with severe mucous plugging. Procedure duration should be minimized. Monitor the patient closely for worsening airway resistance, barotrauma, and hemodynamic instability during the procedure.
- Routine bronchoscopy in patients with severe AECOPD is not beneficial.

Pharmacologic therapy (Table 24.2)

- Bronchodilators:
  - Inhaled β_2-agonist treatments act within 5 minutes to decrease airway inflammation, relax airway smooth muscle, and decrease mucous production. For a patient in respiratory distress, repeated doses may be given at intervals of every 20 minutes to every hour. Continuous nebulization may be required. Administration via a nebulizer or MDI has equivalent effects; however, nebulized treatment is recommended for patients in respiratory distress to ensure adequate medication delivery.
  - Inhaled ipratropium bromide may be added to β_2-agonist therapy to augment the bronchodilator effect. Due to its slow onset of action, it should not be used as a stand-alone bronchodilator.
  - Parenteral methylxanthine administration is generally not recommended in the acute setting.
  - Subcutaneous, endotracheal, or parenteral epinephrine may be considered in patients refractory to inhaled bronchodilator therapy.

Table 24.2 Frequently used medications in acute severe asthma and severe AECOPD.

Drug name	Recommended dosage	Frequency
Nebulized albuterol	2.5 mg to 5 mg	Every 20 minutes initially then every 4–6 hours in the stabilized patient Severe disease may require continuous administration
Nebulized ipratropium	0.5 mg (2.5 mL)	Every 6–8 hours
Nebulized albuterol/ ipratropium	2.5 mg/0.5 mg per 3 mL	Every 4–6 hours
Methylprednisolone	60–125 mg IV	Every 6 hours until stabilized
Magnesium sulfate	2 g IV	One time dose given over 20 minutes
Epinephrine	0.1–0.3 mg subcutaneous	Every 20 minutes (to a maximum of 0.01 mg/kg)
Lorazepam	0.01–0.1 mg/kg/h continuous infusion	Titrate to targeted level of sedation and patient–ventilator synchrony
Midazolam	0.02–0.1 mg/kg/h continuous infusion	Titrate to targeted level of sedation and patient–ventilator synchrony
Morphine	2–30 mg/h continuous infusion	Titrate to targeted level of sedation and patient–ventilator synchrony
Fentanyl	0.7–10 μg/kg/h continuous infusion	Titrate to targeted level of sedation and patient–ventilator synchrony
Propofol	0.3–3 mg/kg/h continuous infusion	Titrate to targeted level of sedation and patient–ventilator synchrony
Cisatracurium	Loading dose: 0.1–0.2 mg/kg Infusion rate: 1–3 μg/kg/min	Titrate to desired train-of-four response

- Corticosteroids:
  - Early corticosteroid administration improves lung function and decreases duration of exacerbation by reducing inflammation and mucous production.
  - Administer methylprednisolone 60–125 mg IV every 6 hours. Transition to lower dosing or oral therapy once symptoms have improved. However, evidence is lacking for benefit of higher dose (>80 mg) or intravenous compared to oral route.
- Antibiotics:
  - Antibiotics should be started in asthmatics with signs and symptoms of bacterial infection.
  - Antibiotics should be administered to COPD patients with moderate to severe exacerbation who meet the Winnipeg criteria (increased dyspnea, increased sputum volume, increased sputum purulence) or who require invasive mechanical ventilation.
  - Antibiotic selection should be based on local bacterial resistance pattern and/or sputum culture results for high risk patients (recent antibiotic use, recent intubation).
- Parenteral magnesium sulfate may have beneficial bronchodilator effects in adult asthmatics with severe airflow limitation. This treatment does not benefit patients with AECOPD.
- Leukotriene-receptor antagonist therapy has not been well studied in patients with acute severe asthma or severe AECOPD. It is not a recommended therapy at this time.
- Mucolytics and chest physical therapy are suitable for asthma and COPD patients with copious or retained secretions. Airway clearance devices may also be beneficial for secretion clearance, but critically ill patients are unlikely to use these effectively.

Refractory respiratory failure in mechanically ventilated patients

- Severe airways disease is dynamic and requires time for treatments to work. Patients may demonstrate respiratory acidosis for 1–2 days.
- If there is lack of response or worsening clinical condition despite above measures, we consider this to be refractory respiratory failure:
  - Hypoxemia despite high FiO_2.
  - Severe persistent hypercapnia ($PaCO_2$ >80 mmHg, pH <7.2).
  - Uncontrolled airway pressures: elevated plateau pressures, auto-PEEP.
  - Inability to achieve tidal volumes due to elevated airway pressures.

Additional treatments for patients with refractory respiratory failure

- *Neuromuscular blockade* may be necessary for patients with ventilator asynchrony, severe auto-PEEP, and poorly controlled airway pressures. Patients must be adequately sedated. The neuromuscular-blocking agent should be discontinued as soon as safely possible.
- *ECMO and $ECCO_2R$* may be considered in patients with acute severe asthma with refractory hypoxemia or hypercapnia and/or hemodynamic compromise.
- *Ketamine* is a parenteral anesthetic used in refractory acute severe asthma as an anticholinergic bronchodilator. Evidence does not demonstrate additional benefit over conventional therapy. There is no indication for its use in AECOPD.
- *Inhaled halogenated anesthetics* (isoflurane, sevoflurane) may be administered for patients with refractory acidosis, life-threatening auto-PEEP, and poorly controlled airway pressures despite maximal therapy inclusive of neuromuscular blockade. Anesthetic agents must be administered by an anesthesiologist. These agents have both direct and indirect bronchodilator effects that should be evident shortly after administration. Current data do not associate use of inhaled anesthetics with improved outcomes. There is no indication for use of inhaled anesthetics in AECOPD.

- *Heliox* (helium) is a low density gas that can be mixed with supplemental oxygen to reduce turbulent flow and increase airflow through constricted airways. The mixture includes only up to 30% O_2, thus is not practical for patients with a greater degree of hypoxemia. Limited data support the routine use of heliox for severe obstructive airways disease. It may be utilized as an adjunctive therapy for difficult to ventilate asthmatics.

Prevention/management of complications

- In patients requiring mechanical ventilation, complications of dynamic hyperinflation – including pulmonary barotrauma and hemodynamic compromise – may occur suddenly and can be life threatening.
  - Pulmonary barotrauma may present with sudden worsening in hypoxemia, hypotension, or clinical exam findings such as: absent or diminished breath sounds, tracheal deviation, subcutaneous emphysema, and jugular venous distension.
  - An acute increase in peak and plateau pressures should also raise suspicion for pulmonary barotrauma.
  - If clinical exam suggests tension pneumothorax with instability, immediate needle compression should be performed as a temporizing measure. Tube thoracostomy must then be placed.
  - In the hemodynamically stable patient, there should be prompt evaluation for pneumothorax with CXR and/or bedside ultrasonography in experienced hands.
  - Bedside tube thoracostomy should be performed for definitive management of pneumothorax.
  - Surgical consultation is recommended for management of pneumomediastinum, pneumoperitoneum, and persistent air leaks.
  - If hypotension is attributed solely to dynamic hyperinflation, a brief apnea trial (30–60 seconds of prolonged exhalation) may be attempted. This should be done under the supervision of a senior clinician.
- Patients should be closely monitored for signs of sepsis or venous thromboembolism.
- Prolonged immobilization while on mechanical ventilation, in conjunction with the use of glucocorticoids, sedatives, and neuromuscular blockade agents, may lead to ICU-acquired weakness. With physical rehabilitation, patients typically recover to their pre-hospitalization functional status.

Special populations

Pregnancy

- Status asthmaticus in pregnancy is rare but poses life-threatening challenges to both mother and fetus.
- Pregnant patients have decreased functional residual capacity, increased airway edema, increased mucous secretion, and reduced respiratory reserve placing them at high risk for respiratory failure.
- Maternal hypoxia must be avoided to prevent intrauterine growth retardation and fetal death. A target PaO_2 of greater than 65 mmHg is considered safe.
- Generally, treatment strategies are the same as in non-pregnant patients but several areas warrant special attention:
  - Short-acting β_2-agonists and corticosteroids are generally considered safe for the treatment of acute severe asthma in pregnancy.
  - The safety of continuous sedative infusion in pregnancy is unknown.
    - Propofol (pregnancy category B) is commonly used and may have additional bronchodilator effects. Caution must be exercised to avoid hypotension. Excessive dosing may lead to decreased uterine smooth muscle tone.
    - Opiates (pregnancy category C) are used for short-term continuous sedation and analgesia in pregnancy. These medications cross the placenta. Longer-term use – or third trimester use – might affect fetal neurologic development or result in neonatal withdrawal syndrome.

    - Benzodiazepines (pregnancy category D) should be avoided. These medications cross the placenta and pose fetal risk.
    - If neuromuscular blockade is required, short-term use of cisatracurium (pregnancy category B) is recommended. Longer term use may result in fetal arthrogryposis.
  - NPPV should be used only in highly selected patients. Pregnant patients are at higher than normal risk for gastric distension and aspiration.
  - Mechanical ventilation in pregnant asthmatics poses particular challenges and should be managed by expert practitioners. The intensivist must work with the obstetrician and maternal–fetal specialist as a team to manage these patients.
  - Permissive hypercapnia strategies may be life-saving, but have not been studied specifically in pregnancy.
    - Due to increased minute ventilation in pregnancy, baseline $PaCO_2$ levels are lower in pregnancy.
    - Higher $PaCO_2$ levels may have deleterious effects, including decreased uterine blood flow and fetal respiratory acidosis.
    - While controversial, permissive hypercapnia has been used successfully with excellent pregnancy outcomes. In pregnant patients with refractory respiratory failure despite aggressive treatment, permissive hypercapnia may be exercised with caution.

Prognosis

Prognosis for treated patients

- AECOPD:
  - Admission for AECOPD is associated with a 1 year mortality of 1–9% with significantly increased rates for patients requiring mechanical ventilation.
  - Several risk factors portend a worse prognosis – severity of underlying COPD, need for long-term oxygen therapy, comorbid conditions, older age – with 1 year mortality rates surpassing 25–40%.
  - Patients who can be managed with NPPV have lower mortality and shorter length of stay.
  - Postextubation, many patients will not return to their baseline respiratory status.
- Acute severe asthma:
  - Patients requiring mechanical ventilation for acute severe asthma have low immediate mortality but maintain a high risk for recurrence of status asthmaticus.
  - Mortality at 1 year has been cited as high as 10% for patients with recurrent acute severe asthma needing intubation.
  - Excluding patients with out of hospital respiratory and cardiac arrest, the majority of patients admitted with acute severe asthma return to baseline functional status.

Follow-up tests and monitoring

- Post-discharge, patients should have prompt follow-up with a pulmonologist.
- Pulmonary function testing should be performed following the exacerbation.
- Patients with AECOPD should be evaluated for pulmonary rehabilitation once they have recovered from the acute phase of disease.
- Several factors require iterative education including: reliable and rapid access to medical care, adherence to medication regimen, appropriate inhaler therapy technique, understanding signs and symptoms of exacerbation, monitoring increased use of rescue medications, and trigger avoidance.

Reading list

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Guidelines

National society guidelines

Title	Source	Date and weblink
National Asthma Education and Prevention Program: Expert panel report III – Guidelines for the Diagnosis and Management of Asthma	National Heart, Lung, and Blood Institute	2007 http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
Standards for the Diagnosis and Management of Patients with COPD	American Thoracic Society/European Respiratory Society Task Force	2004 https://www.thoracic.org/statements/copd.php
International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma: Allergy and Asthma	American Thoracic Society/European Respiratory Society Task Force	2014 https://www.thoracic.org/statements/resources/allergy-asthma/Severe-Asthma-CPG-ERJ.pdf

International society guidelines

Title	Source	Date and weblink
GINA Report: Global Strategy for Asthma Prevention and Management	Global Initiative for Asthma	2020 www.ginasthma.org
Global Strategy for the Diagnosis, Management and Prevention of COPD	Global Initiative for Chronic Obstructive Lung Disease	2020 www.goldcopd.org

Images

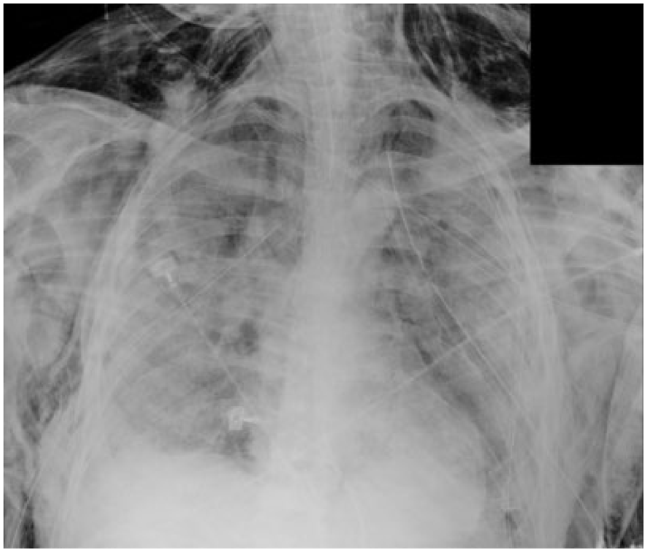

Figure 24.1 Barotrauma in a patient with status asthmaticus. Patient has extensive subcutaneous emphysema and required chest tubes for bilateral pneumothorax.

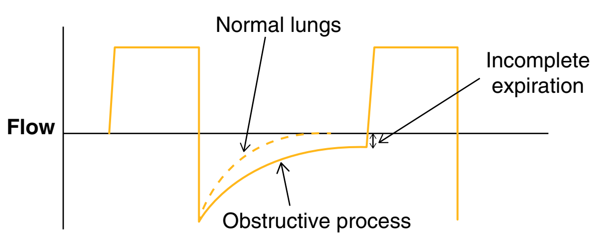

Figure 24.2 Flow versus time tracing showing optimization of prolonged expiratory phase so that expiratory flow reaches zero before the next inhalation (dashed line).

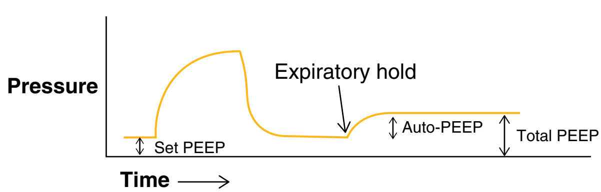

Figure 24.3 Pressure versus time profile demonstrating auto-PEEP using an expiratory hold maneuver.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 25

Weaning from Mechanical Ventilation

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OVERALL BOTTOM LINE

- An aggressive and protocolized approach to ventilator weaning will lead to decreased duration of mechanical ventilation and subsequent decreased morbidity and mortality.
- Patients should be assessed daily for weaning readiness.
- The best method to determine if patients are ready to breathe spontaneously is to perform a spontaneous breathing trial.
- Approximately 15% of patients, who are weaned from mechanical ventilation and extubated, require reintubation within 48 hours.

Background

- Mechanical ventilation can be a life-saving intervention in the critically ill patient. However, intubation and mechanical ventilation are not without risk.
- Complications of mechanical ventilation can be serious and include hemodynamic disturbances, VAP, tracheal injury, gastrointestinal stress ulcers with bleeding, skin breakdown and pressure ulcers, muscle wasting and acquired weakness, barotrauma, pain and discomfort.
- The aim of the intensivist, therefore, should be to utilize mechanical ventilation for whatever duration necessary and not a day longer.
- While focus should appropriately be on reversing the cause of respiratory failure, it must also be on maintaining homeostasis of the other systems, e.g. fluid balance, mental status, muscle strength.
- About 20–40% of mechanically ventilated patients fail their first attempt at weaning. More than half of the total duration of mechanical ventilation can be spent in the weaning process.
- Premature extubation requiring reintubation has been shown to increase mortality from 2.5 to 10 times compared with patients who do not require reintubation.

Definition

- Ventilator weaning, also known as liberation, refers to the process of discontinuing mechanical ventilation and involves two components:
  - Assessment of readiness to wean from mechanical ventilation: determine whether the patient meets prespecified weaning readiness criteria to assess if he/she can be safely removed from the ventilator.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- Weaning: this is the process of structured decrease in mechanical ventilation support and liberation from the mechanical ventilator. Some patients can be immediately shifted to spontaneous ventilation or a spontaneous breathing trial, for others it may be a progressive transition.

Incidence/prevalence

- Approximately 800 000 hospitalizations require mechanical ventilation per year in the USA. This accounts for roughly 3% of hospital admissions.
- It is estimated that there are 2.7 episodes of mechanical ventilation per 1000 population.

Assessment of readiness to wean

- Before weaning can begin, the causes of respiratory failure must be addressed.
- Respiratory failure, simplified, is an imbalance in strength versus load, where the work of breathing (load) exceeds the capacity of the patient to maintain it (strength).
- Failure is often due to a combination of changes in both strength and load; each can be comprised of multiple factors.
- Weaning will be successful when the balance is restored in favor of strength.

Factors that affect respiratory strength and load

Impair strength	Increase load
Corticosteroids	Obesity
Paralytics	Airway obstruction
Malnutrition	Decreased lung compliance (consolidation/congestion)
Sepsis	Sepsis
Advanced age	Increased dead space (pulmonary embolism)
Neuromuscular weakness	Chest wall abnormalities
Hypothyroidism	Increased metabolism (fevers)
Prolonged bedrest	Metabolic acidosis

- The cause of respiratory failure must be treated and resolving.
  - Antibiotics for pneumonia, systemic corticosteroids/bronchodilators for asthma/COPD exacerbation, diuresis for heart failure, and allowing sufficient time for the underlying acute process to improve.
  - Such measures will lead to improved compliance and resistance via mechanisms such as reducing pulmonary edema, resolving atelectasis and pleural effusions, dilating airways, and reducing auto-PEEP and dynamic hyperinflation.
  - What precipitates respiratory failure is not necessarily what maintains it. An example would be muscle atrophy, in particular the diaphragm, which occurs over the course of intubation. This has been shown to occur within hours of the onset of controlled mechanical ventilation.
- When the inciting event stops progressing and begins to regress, assessment for weaning should begin.

Maintaining homeostasis of the other systems

- Maintenance of homeostasis of systems outside the respiratory system is essential to successful ventilator weaning. These other systems include but are not limited to the neurologic, cardiovascular, and neuromuscular systems.

- In the past, patients had been kept sedated, immobile (sometimes paralyzed), and on full ventilator support for the duration of their acute illness.
- We now understand that we need to be as aggressive with weaning (off) as we are with supportive interventions (on). The following are now standard best practices, a number of which have been shown to reduce the duration of mechanical ventilation.

Daily sedation interruption

- Continuous sedation deprives the physician of a vital assessment tool in the evaluation of ventilator weaning: the patient's mental status. This can lead to overestimation of the patient's level of illness, underestimation of strength, as well as prolonged immobilization.
- In the vast majority of patients, a daily sedative hold with re-initiation only if necessary (and at half the dose) has been shown to decrease the duration of intubation.
- In a landmark study, a daily sedative hold reduced the duration of mechanical ventilation by an average of 2.4 days.

Daily spontaneous breathing trial

- A spontaneous breathing trial (SBT) should be performed daily on ventilated patients who meet prespecified weaning readiness criteria; this SBT is ideally performed during a sedation hold.
- In addition to allowing for assessment of weaning readiness, a SBT may prevent the atrophy of the diaphragm and chest wall muscles.

Fluid restriction

- Positive fluid balance can lead to pulmonary congestion, decreased lung compliance, and increased respiratory load.
- In hemodynamically stable patients, a net-even fluid balance should be targeted. This approach was shown to reduce mechanical ventilation duration without increasing the incidence of circulatory shock or the need for dialysis.

Early initiation of physical therapy

- With each passing day immobilized in bed, a patient becomes weaker. The muscles of the respiratory system are not spared.
- Immobilization can also perpetuate the idea that a patient is not capable of unsupported breathing, i.e. they look sicker than they are.
- Early mobilization was shown to reduce the duration of mechanical ventilation as well as improving physical and cognitive functions.
- Mechanically ventilated patients, who are at baseline functional independence, and meet criteria for cardiopulmonary stability, should participate in physical and occupational therapy as early as possible.

Nutrition

- Malnutrition plays a role in patient weakness, and becomes cumulative over the course of an ICU stay. This is potentiated by the hypercatabolic state of the critically ill patient.
- While there is ongoing debate as to the timing of initiation of nutrition, maintaining caloric intake, including fat and protein, is necessary to prevent further weakness.
- Hypokalemia, hypophosphatemia, and hypomagnesemia all cause muscle weakness and should be corrected.

Acid–base status

- Some patients have a chronic component of respiratory failure, such as chronic respiratory acidosis in COPD or obesity hypoventilation syndrome. These patients will never be able to tolerate physiologically

normal bicarbonate levels, as they cannot maintain the necessary minute ventilation to keep a normal serum pH.

- For these patients, trying to achieve a 'normal $PaCO_2$' will lead to wasting of appropriately retained bicarbonate. Therefore, the physician should accept bicarbonate retention and hypoventilation at baseline levels and not target a normal arterial blood gas prior to extubation.

Assessment of readiness for extubation

- Once weaning has commenced, patients should be assessed for possible extubation each day. The assessment includes:
  - Respiratory parameters – demonstrating the ability to breath spontaneously with minimal ventilator support and supplemental oxygen requirements.
  - Hemodynamic status – shock resolving, not requiring high doses of vasopressors.
  - Mental status – able to protect the airway.
- The standard for assessing the patient's readiness for extubation is an SBT.
- An SBT should be attempted when the above criteria are met. Waiting to initiate SBTs when the physician feels confident that extubation will be successful will delay extubation.
- A patient who completes a successful SBT should be assessed for extubation if he/she can protect his/her airway without an endotracheal tube in place.

Spontaneous breathing trials

- The SBT is an unassisted to minimally assisted period of breathing while the patient remains intubated.
- The SBT consists of placing the patient on a T-piece, CPAP (typically 5 cmH_2O), or low level pressure support (5–8 cmH_2O or less above PEEP) for a period of 30 minutes to several hours daily.
  - These modes have been shown to be superior to higher levels of pressure support or synchronized intermittent mandatory ventilation (SIMV).
  - Circumstances may require that an SBT is extended, but neither increased duration nor increased frequency of the SBT has been shown to add predictive power when compared with at least 30 minutes once a day.
  - Note that even low levels of pressure support and PEEP can significantly augment work of breathing, and therefore mask ongoing respiratory failure.
  - Arguments have been made for the T-piece as the 'truest' assessment of a patient's capacity for spontaneous breathing at atmospheric pressure.
  - The physician should be aware of the cardiac augmentation that CPAP or pressure support provides, and account for this in patients with heart failure.

Methods of SBTs

Continuous positive airway pressure

- CPAP provides a minimal static pressure that prevents atelectasis while allowing for relatively unassisted breathing. Proponents of CPAP argue that it increases functional residual capacity and maintains small airway patency, while not masking work of breathing.
- A CPAP trial occurs while the patient is connected to the ventilator, providing a means of monitoring with alarms in place.
- Spontaneous breathing trials using CPAP or a T-piece have been shown to decrease the duration of intubation, as compared with a graduated weaning of pressure support and SIMV.
- CPAP will not compensate for the resistance of the endotracheal tube, and can lead to a failed SBT in an otherwise capable patient if the tube is narrow.

Pressure support ventilation

- Pressure support ventilation (PSV) is a mode which is patient triggered, flow cycled, and pressure limited, usually combined with CPAP.
- Like CPAP, it does not require disconnection from the ventilator, and apnea alarms and pressure monitors remain in place.
- PSV can also overcome the increased resistance of narrower endotracheal tubes.
- The drawback of pressure support is that it augments the respiratory muscles of inspiration in direct proportion to the amount of support employed, which can mask ongoing respiratory failure.
  - For example, pressure support of 5 cmH_2O over PEEP 5 cmH_2O is equivalent to bilevel non-invasive pressure support IPAP 10/EPAP 5 (assuming adequate seal), a level that is often used to rescue patients from respiratory failure.

T-piece/T-tube

- A T-piece trial involves disconnecting the endotracheal tube from the ventilator and attaching it to a tube that is connected to humidified oxygen. This tubing extends beyond the endotracheal tube, forming a 'T' and allowing for a reservoir of oxygen (Figure 25.1).
- The T-piece trial is simple, well tested, and imposes a pulmonary workload that is comparable to that encountered after extubation.
- Initially, there were concerns that the T-piece led to an increase in the work of breathing as compared with the extubated airway due to the resistance provided by the endotracheal tube.
- These studies did not account for the airway inflammation and edema that persist after extubation, however, which results in little difference between the pre-extubation and post-extubation airway diameter and thus workload.
- Unlike positive pressure, a T-piece does not reduce venous return or reduce the left ventricle afterload and therefore will not mask heart failure.
- A drawback of the T-piece is that the patient needs more frequent monitoring as they are disconnected from the ventilator without its associated alarms.
- With smaller diameter endotracheal tubes (≤7 mm) resistance can exceed even that of the post-extubation airway.

Criteria for a successful SBT (Table 25.1)

- After 30–120 minutes of an SBT the patient should be evaluated for work of breathing. To be considered a success, the patient should be breathing comfortably without signs of respiratory distress (excessive tachypnea or use of accessory muscles of respiration).
- Other important criteria for extubation include:
  - Hemodynamic stability.
    - Patients who develop significant hypertension or hypotension or significant tachycardia or bradycardia should not be extubated.
  - Ability to protect the airway.
    - Patients with subdued level of consciousness, poor gag reflex, or excessive respiratory secretions are likely to aspirate and require reintubation.
      - Extubation in such patients should be attempted on a case-by-case basis, taking into account the reversibility of the underlying process and engaging in patient/family education as to the risk of reintubation.
      - In these patients, tracheostomy is an alternative option.
  - Oxygen requirements that can be provided by non-invasive modalities.
    - Usually an FiO_2 ≤0.5 to maintain saturation >90%.

Table 25.1 Criteria for a successful SBT.*

Clinical assessment
Cause of respiratory failure is improving Mental status awake, alert, or easily arousable and following commands No signs of accessory muscle use, abdominal breathing, diaphoresis, sensation of dyspnea, or general distress
Objective measures
Respiratory: Respiratory rate less than 35/min, greater than 8/min SpO_2 >90% on FiO_2 ≤50% RSBI <105
Cardiovascular: Hemodynamic stability or on low dose vasopressor Blood pressure and heart rate within 20% of pre-SBT No evidence of myocardial ischemia or onset of arrhythmia

* These criteria are individualized, as some patients may not be expected to follow commands. Some patients may have chronic respiratory failure and not fulfill usual respiratory parameters.

    - Resolution of the obstruction, if upper airway obstruction was the indication for intubation.
        - In these patients, a cuff leak test should be performed. This involves deflating the endotracheal tube cuff and listening for laryngeal airflow, as well as looking for a discrepancy between measured inspiratory and expiratory tidal volumes on the ventilator. The cuff leak test (with a leak of >110 mL) can be utilized as a means to predict lack of post-extubation stridor. This leak test has been applied to patients with airway edema. Although not definitive as a criterion for extubation, absence of a leak can indicate that obstruction has not resolved.
    - Manageable secretions.
        - Voluminous secretions, especially in a patient with decreased level of alertness, can lead to inability to clear the airways and reintubation.
    - RSBI <105.
        - In addition to bedside clinical evaluation, a scoring system has been developed that is predictive of extubation failure. The RSBI has been used both in assessing readiness to wean and in evaluating the success of the weaning trial itself.
        - RSBI is the respiratory rate divided by the tidal volume (in liters).
        - A number higher than 105 (breath/min/L) is highly predictive of failure (sensitivity 0.97).
        - A number lower than 105 is moderately predictive of success (specificity 0.64). The lower the number, the greater the likelihood of success. This correlates with a lower respiratory rate and a larger tidal volume which simulates normal, relaxed breathing.
        - The trend, rather than an individual value, of RSBI may be a better predictor of weaning success.
- Most patients will require minimal to no weaning off ventilatory support and are extubated without difficulty after their first SBT.
- Diaphragm atrophy has been demonstrated in an autopsy study of patients receiving mechanical ventilation. Thinning of the diaphragm (based on ultrasound studies) has been shown during the course of mechanical ventilation. For this reason, some clinicians favor a mode of breathing that preserves spontaneous respiratory effort.
    - Examples would include patients with upper airway obstruction (e.g. angioedema) or patients who breathe comfortably on higher levels of pressure support.
    - Such patients can be maintained on a spontaneous mode of ventilation as long as they are breathing comfortably.

- Many patients who meet some but not all of the criteria for weaning will still be liberated successfully. Clinicians frequently underestimate a patient's likelihood of success, and failure of an SBT in most patients is less injurious than not attempting one at all.
- The SBT is ideally done during a sedation hold, when the patient is awake and interactive. This is not always feasible.

Weaning protocols

- Weaning protocols are instituted in many ICUs to ensure that all intubated patients are evaluated on a daily basis for readiness to wean.
- Implementation of a daily weaning protocol has been shown to reduce the duration of mechanical ventilation, ventilator-associated pneumonia, self-extubation rates, tracheostomy rates, and cost.
- Weaning protocols are often used in combination with sedation protocols. The goal is daily interruption of sedatives or maintaining patients in an alert, comfortable state so that weaning can progress and extubation performed at the earliest moment.
- A respiratory therapist-led or nurse-led protocol generally incorporates the following:
  - Daily early assessment of each patient for weaning readiness, based on specific criteria for respiratory status, hemodynamic stability and mental status.
  - Initiate weaning mode for specified time.
  - Assess tolerance of SBT.
  - ICU team makes decision for extubation.
- Lack of a weaning protocol and delays in advancing the weaning process are associated with increased morbidity and mortality.

Extubation

Once the decision is made for extubation, the process proceeds as follows:

- Enteral tube feedings should ideally be held for 2 hours prior to extubation.
- Explain to the patient what is going to happen.
- Supplemental oxygen and humidified air set up.
- Position the patient appropriately in the sitting-up position, if possible.
- NPPV on standby if indicated for a patient at high risk of extubation failure (heart failure, obesity).
- Suction the mouth and trachea to remove retained secretions.
- Deflate the endotracheal tube cuff.
- Remove the endotracheal tube.
- Examine the patient for increased work of breathing and stridor. Ongoing monitoring of vital signs.

Extubation failure

- Approximately 10–20% of patients fail extubation despite a successful SBT. A failed extubation does not mean the decision to extubate was wrong.
- Factors shown to increase the risk of failed extubation despite passing an SBT include: net positive fluid balance in the prior 24 hours, pneumonia as the cause of respiratory failure, inadequate cough, poor mental status, and a higher RSBI score.
- Failure typically manifests as increased work of breathing as evidenced by accessory muscle use, tachypnea, tachycardia, and anxiety.
- Prolonged post-extubation failure can lead to shallower breathing and decreasing alertness.
- Patients should be examined for stridor; inspiratory stridor indicates a narrow upper airway, increased airway resistance, and turbulent flow.
- Extubation failure requiring reintubation is associated with worse outcomes, including increased mortality, length of stay, and transfer to a long-term care facility.
- Delaying reintubation in patients who are failing has been shown to further increase mortality.

Management of extubation failure

- The patient showing signs of failure after extubation should be considered for reintubation as early as possible. Patients at high risk of extubation failure should be considered for NPPV or high flow oxygen therapy after extubation.
- Good candidates for a trial of NPPV include patients with COPD as the cause of respiratory failure, a patient who is awake, strong, and able to protect their airway, patients who have a rapidly reversible cause of persistent increased work of breathing (residual pulmonary vascular congestion responsive to a diuretic), or those with mild work of breathing that easily resolves with NPPV.
- Regardless of the underlying factor(s), if the patient is not rapidly rescued by non-invasive ventilation, reintubation should not be delayed, as prolonged failure prior to reintubation increases mortality.
- For stridor: nebulized racemic epinephrine (0.5 mL of a 2% solution diluted in a volume of 2–4 mL), methylprednisolone 40 mg IV, and a trial of NPPV can improve airflow and may prevent reintubation. For severe stridor or deteriorating vital signs, reintubation should be done immediately.

Risk factors for extubation failure

- Older patients.
- Severity of illness on ICU admission.
- Prolonged ventilation.
- Weak cough.
- Failure of multiple SBTs.
- Pre-existing left ventricular dysfunction.
- Positive fluid balance (in the prior 24 hours)
- Pneumonia as the cause of respiratory failure.
- Altered mental status.
- Higher RSBI score.
- Upper-airway obstruction.

Managing the difficult to wean patient

Not all patients will pass their SBT and be ready for extubation on their first attempt. For these patients, ongoing management of the cause of failure, continued work on improving strength/load parameters, and frequently just passage of time will eventually lead to a successful SBT and extubation. Alternatively, a subset of patients may benefit from early extubation to NPPV.

Role of non-invasive ventilatory support in weaning

- Non-invasive positive pressure ventilation (BIPAP or CPAP) can be used immediately after extubation in selected patients who show borderline parameters during their SBT but are deemed likely to tolerate extubation with pressure support.
- Such patients include those with COPD, resolving heart failure, and patients with marginal RSBI scores.
- These patients should have good mentation, be capable of protecting their airway, and should be able to clear their secretions.

Role of tracheostomy

- A subset of patients has no hope of weaning (e.g. persistent neurologic injury) or has a prolonged course of endotracheal intubation. In these patients, tracheostomy may be indicated.
- Tracheostomy can be an integral part of the weaning process and is not necessarily an endpoint in itself.
- Tracheostomy can facilitate weaning by reducing dead space and decreasing airway resistance (which improve work of breathing), augmenting secretion clearance, and improving patient comfort (which reduces the need for sedation). Studies have shown reduced rates of ventilator-associated pneumonia.
- Tracheostomy provides a more secure airway and allows for greater participation in physical therapy and mobilization.
- Superiority of early versus late (at 2 weeks) tracheostomy has not been shown.
- The timing of tracheostomy remains controversial and no clear consensus has been reached on early versus delayed tracheostomy in most ICU patients.

Other factors to consider

Agitation

- Patients frequently suffer from disorientation that occurs upon sedative withdrawal, delirium from a prolonged ICU course, and pain from catheters and the endotracheal tube. This can lead to anxiety, tachypnea, and shallow and dyssynchronous breathing.
- In this case, a small amount of sedation can relieve the agitation and allow the physician to differentiate what is true work of breathing from mere agitation. If the patient tolerates the SBT with this sedation, then the physician should proceed with extubation.

Obesity

- Obesity decreases chest wall compliance and functional residual capacity. When intubated and passively ventilated, this can lead to atelectasis and hypoxia. For this reason, obese patients may require increased PEEP for adequate oxygenation despite resolution of the cause of respiratory failure. This can exaggerate their ventilator and oxygen requirements.
- Once extubated and actively breathing, they will often recruit lung and oxygen saturation will improve.
- NPPV can ameliorate post-extubation atelectasis.

Persistent hypoxia despite decreased work of breathing

- Some patients pass an SBT, yet continue to have significant hypoxemia with a high FiO_2 requirement, indicative of shunt physiology. An example would be resolving pneumonia.
- In such patients extubation to HFNC will allow for a high FiO_2 without requiring invasive ventilation. HFNC is capable of providing FiO_2 at levels as high as 80–90%, even with patients who have a high minute ventilation.
- Older and smaller individuals often breathe at lower tidal volumes. This decreases the sensitivity of the RSBI for predicting successful extubation.

Ventilator factors

- Problems with the ventilator and endotracheal tube can lead to a patient failing their SBT despite adequate respiratory function.
  - Examples include kinked tubing, endotracheal tube narrowing secondary to precipitated secretions (Figure 25.2), fluid in tubing, and equipment dead space. This should be investigated in patients without a clear reason for failing their breathing trial.
  - Indicators of an obstructed endotracheal tube include difficulty passing the suction catheter and ventilator flow waveforms of a fixed upper airway obstruction.

CLINICAL PEARLS

- Anticipation of and preparation for weaning and extubation should begin from the moment of intubation.
- Respiratory failure is an imbalance of strength and load. Extubation will be successful when the balance is restored in favor of strength.
- Maintaining homeostasis of other systems is as important as reversing the initial cause of respiratory failure.
- The daily SBT is the most effective weaning method. With few exceptions, every patient should have a daily SBT.
- Be aggressive, if all of your extubations are successful than you are waiting too long.
- Daily assessment for weaning as part of a weaning protocol improves identification of patients and weaning from mechanical ventilation.
- In certain circumstances, NPPV after extubation can be used to expedite liberation from the ventilator.
- If a patient fails a SBT, make sure the ventilator is not the reason.

Reading list

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Images

Figure 25.1 T-piece.

Figure 25.2 Impacted endotracheal tube: tube cut with axial view. Note significantly reduced airway radius.

Additional material for this chapter can be found online at:
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PART 4

Neurologic Critical Care

Section Editor: Stephan A. Mayer

CHAPTER 26

Delirium

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OVERALL BOTTOM LINE

- Delirium is common in hospitalized patients, and particularly in the ICU.
- Delirium is associated with increased mortality and morbidity.
- Delirium may be a manifestation of a reversible medical problem.
- Prevention of delirium is possible with careful management of modifiable factors.
- Early recognition and treatment is crucial to reduce the negative sequelae of delirium.

Background

Definition of disease

- Delirium is a syndrome characterized by a disturbance in attention and awareness; associated with a change in cognition that is not better accounted for by a pre-existing, established, or evolving dementia. The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day (DSM-5).
- Delirium may also be divided into subtypes based on the pattern of symptoms: *hyperactive*, *hypoactive*, and *mixed*:
  - Patients with hyperactive delirium demonstrate features of restlessness, agitation, and often experience hallucinations and delusions.
  - Patients with hypoactive delirium present with lethargy and reduced spontaneity, and show little spontaneous movement.
  - A mixed presentation may include features of both hyperactive and hypoactive delirium.

Incidence/prevalence

- Delirium occurs in approximately 20–50% of general hospital inpatients, and 40–80% of patients admitted to the ICU.
- Delirium is more common in patients who are elderly and have cognitive impairment.

Etiology

Common triggers of delirium include, among many others:

- An underlying systemic infection or decompensated medical condition.
- Drug exposure or withdrawal.

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- Pain.
- Sleep deprivation.
- Metabolic and electrolyte disturbances.

Pathophysiology

There have been multiple mechanisms proposed to explain the pathophysiology of delirium. Neurotransmitter dysfunction appears to play a role; namely decreased cholinergic activity, as well as serotonin imbalance. An abnormal central nervous system response to inflammatory mediators, including increased microglial activation, may also contribute to delirium.

Prevention

BOTTOM LINE

- Prevention is exceedingly important and overlaps with management strategies for delirium.
- Prevention involves identifying patients with predisposing risk factors to develop delirium. A multidisciplinary approach is then required to address preventable risk factors and to institute effective positive measures, including frequent reorientation, promotion of normal sleep, exposure to sunlight, and attention to pain and overall comfort.
- There is evidence that dexmedetomidine is associated with a lower risk of delirium than midazolam.
- There is evidence that bispectral index (BIS) guided anesthesia may reduce the incidence of delirium compared with BIS-blinded anesthesia or clinical judgment.

Important risk factors for delirium

Unmodifiable risk factors	Potentially preventable risk factors
Advanced age	Hearing/vision impairment (glasses, hearing aids)
Apolipoprotein E4 genotype	Electrolyte abnormalities
History of hypertension	Anemia
Alcohol use	Fever
Tobacco use	Lack of visitors
Pre-existing cognitive impairment	Inadequate pain management
History of depression	Sedatives
High severity of illness	Immobility
Need for mechanical ventilation	Catheters
Elevated inflammatory markers	Gastric tubes
High LNAA (large neutral amino acid) metabolite levels	Sleep deprivation
	Dehydration
Isolation	Inadequate light
Need for multiple infusing medications	Lack of BIS-guided anesthesia

Diagnosis

Typical presentation

- An elderly man with a history of mild dementia is admitted to the ICU after spine surgery. On postoperative day 2, he appears more confused than usual and is combative with the nursing staff.

Validated tools to aid in the diagnosis of delirium

- Delirium is often unrecognized in critically ill patients without the use of an instrument to aid in the diagnosis.
- Multiple validated tools exist to assess delirium in critically ill patients (Table 26.1).

Table 26.1 Screening tools for delirium.

Screening tool	Method	Diagnostic criteria
Confusion Assessment Method for the ICU (CAM-ICU)	Feature 1: assess for acute change in mental status, fluctuating behavior or serial Glasgow Coma Scale (GCS) score or sedation ratings over 24 hours Feature 2: assess using picture recognition or random letter test Feature 3: assess by asking the patient to hold up a certain number of fingers Feature 4: rate level of consciousness from alert to coma	Features 1 or 2 are positive, along with either feature 3 or feature 4
Intensive Care Delirium Screening Checklist (ICDSC)	Checklist of eight items: • Altered level of consciousness • Inattention • Disorientation • Hallucination or delusion • Psychomotor agitation or retardation • Inappropriate mood or speech • Sleep/wake cycle disturbance • Symptom fluctuation	Positive if score is ≥4
Abbreviated Cognitive Test for Delirium (aCTD)	Total score obtained by summing up two content scores: attention (range 0–14) and memory (range 0–10) Attention is assessed using the visual memory span subtest of the Wechsler Memory Scale Revised Memory is assessed by recognition of pictured objects	Positive if score is <11
Neelon and Champagne Confusion Scale (NEECHAM)	The scale is divided into three subscales: • Information processing (attention, processing, orientation) • Behavior (appearance, motor and verbal behavior) • Physiologic condition (vital function, oxygen saturation, urinary incontinence)	Moderate–severe: 0–19 Mild: 20–24 High risk: 25–26 No delirium: >26 (Scale out of 30)
Delirium Detection Score (DDS)	Checklist of eight items: • Agitation • Anxiety • Hallucination • Orientation • Seizures • Tremor • Paroxysmal sweating • Altered sleep–wake rhythm	Positive if score is >7
Nursing Delirium Screening Scale	Checklist of five items: • Disorientation • Inappropriate behavior • Inappropriate communication • Illusions/hallucinations • Psychomotor retardation	Positive if score is >1

- Regardless of the screening tool utilized, it is important foremost to screen for delirium in the ICU.
- Sensitivities for these screening tools vary related to different levels of training and experience amongst assessors, as well as heterogeneity of patient populations.
- When delirium screening is applied, clinical benefits that may ensue include shorter duration of mechanical ventilation, shorter LOS, and lower mortality.
- Similarly, a screening protocol for delirium is associated with significant cost savings.

Evaluation

Delirium may be a manifestation of a reversible medical problem. It is important to identify and treat possible medical and neurologic causes of delirium.

Common triggers of delirium

- Hypoxia, hypercarbia.
- Hypoglycemia, hyperglycemia.
- Electrolyte disorders, acid–base disorders.
- Sepsis.
- Renal failure.
- Liver failure.
- Infection.
- Intoxication.
- Drug withdrawal.
- Medication side effects.
- Hemodynamic instability.
- Stroke.
- Seizure.
- Encephalitis.
- Posterior reversible encephalopathy syndrome.

Laboratory diagnosis

Although various markers have been correlated to delirium, no laboratory test has been found to be useful as a diagnostic test.

Potential pitfalls/common errors made regarding diagnosis of disease

- Suboptimal use of preventive measures, which are essential to reduce the occurrence of delirium.
- Lack of awareness and early use of screening tools for the diagnosis of delirium.
- Failure to adequately review medications and differential diagnosis for medical causes of delirium.

Treatment and management

Treatment rationale

- Delirium is best avoided by early measures targeted at prevention.
- Prevention and supportive management includes mobilization, removal of catheters, and pain control.
- Adequate analgesia is essential, as is judicious use of sedation.
- Weaning from mechanical ventilation should be pursued early and aggressively as deemed medically safe.
- Geriatric consultation may be beneficial in the management of elderly patients with multiple comorbidities and complex medication regimens.

Medications

- Melatonin may assist with sleep regulation.
- Benzodiazepines are useful in alcohol withdrawal, although in general it is best to avoid benzodiazepines as they may worsen delirium.

- Haloperidol (<3.5 mg/day), risperidone (0.5–3 mg/day), and olanzapine (2.5–12.5 mg/day) are equally effective in treating delirium, with few adverse effects. Care should be taken to monitor QTC interval with electrocardiograms in patients treated with these agents.

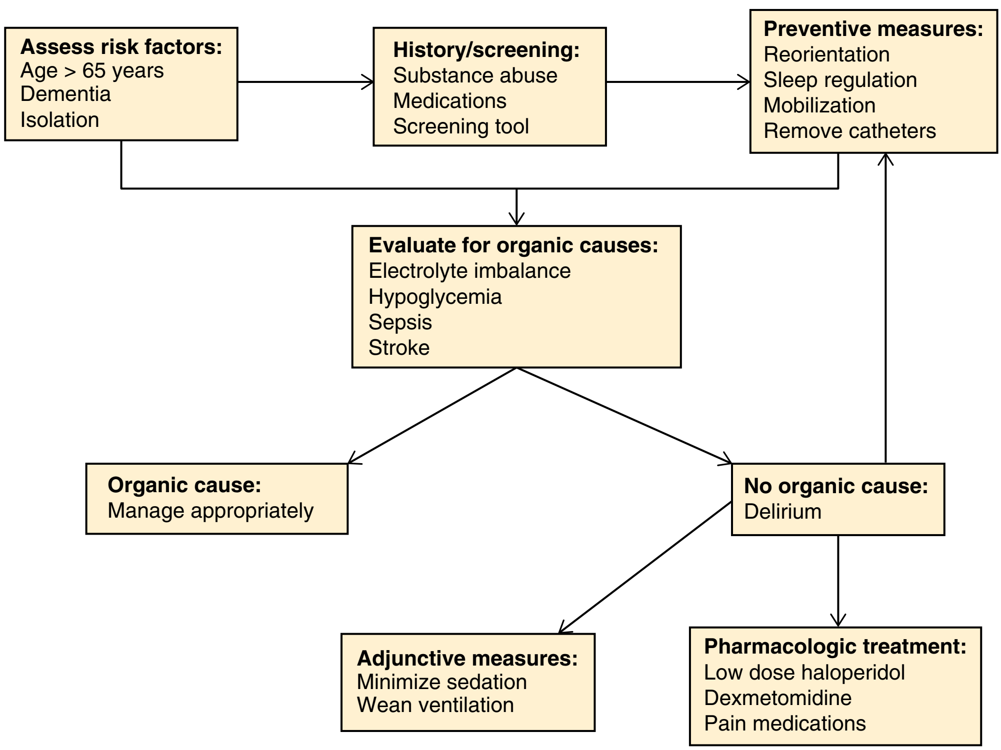
Dexmedetomidine

Use of Dexmedetomidine (0.4–1.4 µg/kg/h) resulted in more ventilator-free days in agitated delirium, and is useful as a rescue drug for agitation in non-intubated patients in whom haloperidol has failed.

- Dexmedetomidine in liver transplant recipients with postoperative delirium decreased ICU length of stay and the dose of supplemental midazolam as compared with haloperidol.
- Dexmedetomidine is associated with bradycardia and hypotension.

Management/treatment algorithm (Algorithm 26.1)

Algorithm 26.1 Management of delirium in the ICU



Specific populations

Pregnancy

- Medications are considered adjunctive. Should pharmacologic treatment be deemed necessary, medications should be used with caution.
- Haloperidol is pregnancy category C. Dexmedetomidine does not appear to cross the placental barrier, although data are limited.

Prognosis

- Delirium is associated with multiple complications and adverse outcomes including self-extubation and removal of catheters.
- Delirium contributes to a prolonged hospital and intensive care length of stay, as well as increased mechanical ventilation duration.
- Mortality risk is 2–3 times higher for critically ill patients who develop delirium.
- Studies have linked delirium to development of cognitive impairment after hospital discharge.

Reading list

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Stevens R, Sharshar T, Ely EW. Brain Disorders in Critical Illness. UK: Cambridge University Press, 2013.

Suggested websites

www.icudelirium.org

Guidelines

National society guidelines

Title	Source	Date and weblink
Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit	Society of Critical Care Medicine (SCCM)	2018 https://www.sccm.org/ICULiberation/Guidelines
Practice Guideline for the Treatment of Patients With Delirium	American Psychiatric Association (APA)	2010 https://psychiatryonline.org
Delirium: prevention, diagnosis and management. Clinical guidelines [CG103]	National Institute for Health and Clinical Excellence (NICE)	2010 https://www.nice.org.uk/guidance/cg103

International society guidelines

Title	Source	Date
Evidence and Consensus Based Guideline for the Management of Delirium, Analgesia, and Sedation in Intensive Care Medicine. Revision 2015	DAS Taskforce, multidisciplinary Germany	2015
National Clinical Guideline Centre (UK) Delirium: Diagnosis, Prevention and Management	Royal College of Physicians	2010

Evidence

Type of evidence	Comment	Date and reference
Meta-analysis	Cochrane review of various antipsychotics for management of delirium	2007 Lonergan E, et al. Antipsychotics for delirium. Cochrane Database Syst Rev 2007;2:CD005594
Double-blind RCT	JAMA double-blind RCT comparing dexmedetomidine and lorazepam in management of delirium in mechanically ventilated patients. Dexmedetomidine appeared superior, with more days alive without delirium and more time at target level of sedation	2007 Pandharipande PP, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298(22):2644–53
Prospective cohort	Cohort study validating use of CAM-ICU as a screening tool to accurately diagnose delirium in critically ill patients who are often non-verbal due to mechanical ventilation	2001 Ely EW, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29(7):1370–9
Review	NEJM review article addressing the relationship between pain management, sedation, and delirium in the ICU	2014 Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med 2014;370:444–54

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CHAPTER 27

Stroke

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OVERALL BOTTOM LINE

- Stroke encompasses three main subtypes: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.
- Acute ischemic stroke comprises the majority (80%) of patients presenting to the emergency department with acute stroke symptoms.
- Prior to 1996, when the FDA approved tissue plasminogen activator (tPA) for use in acute ischemic stroke, there was no available acute treatment.
- Emergency treatments, most notably emergency mechanical thrombectomy for large vessel occlusion, have dramatically affected our ability to reverse stroke symptoms, limit the degree of brain injury, and improve outcomes.

Background

Disease classification

- *Acute ischemic stroke (AIS)*:
  - Cerebral infarction caused by occlusion of a cerebral artery, usually by thrombosis.
  - AIS is usually caused by thromboembolism.
  - Bleeding into an infarct is classified into hemorrhagic transformation (HT) and parenchymal hemorrhage (PH) (Table 27.1).
- *Transient ischemic attack (TIA)*:
  - A transient episode of neurologic dysfunction lasting less than 24 hours caused by temporary focal ischemia.
  - Most TIAs last <30 minutes.
- *Intracerebral hemorrhage (ICH)*:
  - Spontaneous, non-traumatic bleeding into the brain parenchyma or ventricular system.
  - Most ICH is caused by chronic hypertension (Figure 27.1).
- *Subarachnoid hemorrhage (SAH)*:
  - Spontaneous, non-traumatic bleeding into the subarachnoid space.
  - Most cases of SAH are caused by rupture of an intracranial 'berry' aneurysm.

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Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Table 27.1 Classification of hemorrhagic infarction.

Type	Features
Hemorrhagic tranformation (HT) type I	Isolated, scattered petechial hemorrhage
HT type II	Confluent petechiae of blood throughout the infarct, without a space-occupying effect.
Parenchymal hemorrhage (PH) type I:	Confluent hemorrhage limited to ≤30% of the infarcted area with a mild space-occupying effect.
PH type II:	Confluent hemorrhage of ≥30% of the infarcted area with a significant space-occupying effect.

Causes and mechanisms of stroke

- Mechanisms of AIS:
  - Embolism (70%):
    - Cardiac:
      - Atrial fibrillation.
      - Left ventricular thrombus.
      - Atrial septal defect (paradoxical embolism).
        - Aortic atheroma.
    - Artery-to-artery embolism.
    - Embolic stroke of unknown source.
  - Large vessel atherosclerosis (10%):
    - Carotid bifurcation.
    - Intracranial stenosis of internal or middle cerebral artery (MCA).
  - Small-vessel ‘penetrator’ infarction (i.e. lacunar infarction) (10%).
  - Arterial dissection.
  - Systemic hypotension (i.e. ‘watershed’ infarction) (5%).
  - Dural sinus thrombosis (i.e. venous infarction) (3%).
  - Others: non-inflammatory vasculopathies (e.g. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), Moyamoya disease), CNS vasculitis, hypercoaguable states, among others (2%).
- Mechanisms of spontaneous ICH:
  - Hypertension (65%).
  - Amyloid angiopathy (15%).
  - Coagulopathy (15%).
  - Vascular malformation (arteriovenous malformation (AVM), AV fistula, or cavernous hemangioma) (5%).
- Mechanisms of spontaneous SAH:
  - Cerebral aneurysm (80%).
  - Perimesencephalic non-aneurysmal SAH (10%).
  - Intracranial dissection (5%).
  - Sympathomimetic drugs, coagulopathy, or idiopathic (5%).

Incidence/prevalence

Incidence

- Around 795 000 people have a new or recurrent stroke per year, and more than 140 000 people die each year in the USA.
- Worldwide, 15 million suffer a stroke each year, 5 million die and another 5 million are disabled.

- Incidence by type:
  - 85% ischemic (Figure 27.2).
  - 10% intracerebral hemorrhage.
  - 5% non-traumatic subarachnoid hemorrhage.
- On average, every 40 seconds someone in the USA has a stroke.
- Age-adjusted incidence of first ischemic stroke (per 100 000):
  - 0.88 in whites.
  - 1.49 in Hispanics.
  - 1.91 in blacks.

Prevalence

- About 6.6 million Americans >20 years of age have had a stroke, with an overall prevalence of 2.6%.
- Global prevalence in 2010 was 33 million stroke survivors.

Pathophysiology

- Ischemic infarction:
  - Uncoupling of metabolic demand for oxygen and glucose which exceeds delivery.
  - Mitochondrial production of ATP ceases and intracellular ATP stores become depleted rapidly.
  - The ischemic penumbra (zone of tissue between the infarct core and normal brain) experiences reduced blood flow but preserved cellular metabolism. The penumbra is the target for emergency revascularization.
  - As tissue infarcts, cells depolarize, leading to a large influx of calcium and sodium (induced by massive glutamate release, with stimulation of NMDA receptors) and an efflux of potassium.
  - Infarct core cells are destroyed by lipolysis, proteolysis, and disaggregation of microtubules due to metabolic failure.
  - Water moves into the cells following the influx of ions, and cytotoxic edema forms.
  - A secondary inflammatory response occurs in response to cell injury and death, further worsening cerebral edema.
- Cerebral hemorrhage:
  - Disruption of tissue with the expanding hematoma.
  - Direct pressure effects.
  - Inflammatory response.
  - Raised ICP.
  - Hydrocephalus.
- Subarachnoid hemorrhage:
  - Abrupt rise in ICP at time of aneurysm rupture often leads to global hypoperfusion resulting in loss of consciousness, and, in poor grade patients, diffuse brain injury.
  - Obstructive and/or communicating hydrocephalus may occur, compromising level of consciousness, memory, and cognition (Figure 27.3).
  - Delayed arterial vasospasm develops in 70% of patients, and can lead to delayed cerebral ischemia in up to 30% of patients.
- Cerebral venous sinus thrombosis:
  - Venous outflow obstruction due to thrombosis of the venous sinuses may lead to venous infarction, ICH, and raised ICP.

Predictive/risk factors

Ischemic stroke/TIA

- Hypertension.
- Dyslipidemia.
- Diabetes mellitus.
- Atrial fibrillation.

- Diffuse atherosclerotic disease.
- Congestive heart failure.
- Overweight and obesity.
- Physical inactivity.
- Obstructive sleep apnea.
- Cigarette smoking.
- Prothrombotic states.
- Acute MI with LV thrombus.
- Valvular heart disease.
- Migraine.
- Oral contraceptive use.

Intracerebral hemorrhage

- Hypertension.
- Cerebral amyloid angiopathy.
- Anticoagulation and other forms of coagulopathy.
- Chronic alcohol consumption.
- Sympathomimetic drug use.
- Fibrinolytic agents.
- Vasculitis.
- AVM.

Cerebral aneurysm

- Formation:
  - Smoking.
  - Chronic alcohol consumption.
  - Female sex.
  - Hypertension.
  - Family history of first degree relatives with SAH.
  - Inherited diseases:
    - Strong association: autosomal dominant polycystic kidney disease.
    - Weak association: Marfan syndrome, neurofibromatosis I, Ehler–Danlos syndrome, fibromuscular displasia.
- Rupture:
  - Large aneurysm size.
  - History of prior SAH.
  - Smoking.
  - Hypertension.
  - Cocaine and sympathomimetic abuse.

BOTTOM LINE

- Control of risk factors can significantly impact stroke prevention. Careful history-taking and physical examination are needed to address all possible risk factors.
- A multimodal approach to primary and secondary prevention is required for maximal benefit and risk reduction.

Prevention

Screening

- Modifiable risk factor screening: hypertension, diabetes, hyperlipidemia, obesity, smoking, alcohol and drug use, physical inactivity.
- Review history for possible sleep-disordered breathing.
- Atrial fibrillation: arterial pulse assessment followed by ECG in patients >65 years of age.
- Asymptomatic carotid artery disease: consider carotid duplex scanning or other non-invasive imaging in patients at high risk.
- Non-invasive screening for unruptured cerebral aneurysms in family members of SAH patients with ≥1 first degree relative with SAH or an intracranial aneurysm.

Primary and secondary prevention

- Control of risk factors:
  - Hypertension, Diabetes, Hyperlipidemia, Obesity, Smoking cessation.

- Healthy diet and physical exercise: 40 minutes a day 3–4 days per week.
- Limitation of alcohol consumption: ≤2 drinks/day for men and ≤1drink/day for women.
- Carotid artery stenosis (CAS):
  - Daily aspirin and a statin.
  - Asymptomatic: consider carotid endarterectomy (CEA) or stent in patient with >70% stenosis if the risk of peri-operative stroke, MI, and death is low (<3%). CEA or CAS is not recommended in asymptomatic patients >85 years of age.
  - Symptomatic carotid stenosis: consider CEA or CAS for >70% stenosis in younger patients, while CEA is recommended for patients >70 years of age.
- Atrial fibrillation: if the CHA2 DS2-VASc score is 2 or higher anticoagulation is recommended (distinguish valvular versus non-valvular AF).
- Antiplatelet therapy:
  - Primary prevention:
    - Aspirin: daily aspirin 81 mg/day or higher is recommended in patients with high cardiovascular risk (10 year risk >10%).
    - Cilostazol may be used for the prevention of stroke in people with peripheral artery disease.
  - Secondary prevention
    - Short-term combination therapy with aspirin plus clopidogrel may be considered for 21 days, or up to 6 months post stroke/TIA, then resuming single agent therapy.

Diagnosis

Differential diagnosis of acute ischemic stroke

Differential diagnosis	Features
Seizure	Eyes often look towards the hemiplegia rather than away, symptoms may 'march' from one limb to another, focal twitching may be noted, and may be globally impaired
Hypo- or hyperglycemia	May mimic stroke, but may have also features of global impairment, diaphoresis, or nausea
Mass/tumor	May mimic stroke; brain imaging required to distinguish
Hypertensive encephalopathy	Often have blurred vision, may be delirious without specific focal findings
Migraine	Symptoms may be associated with headache, and fluctuate. May have also more global impairment
Conversion disorder	Neurologic exam usually has non-physiologic features
Subdural/epidural hematoma	May mimic acute stroke – CT imaging is required to distinguish this
Other toxic or metabolic encephalopathy	Patient may appear more globally impaired and have tremors or myoclonus, with or without a specific focal deficit

Typical presentation

- **Ischemic stroke or ICH:** acute onset of new focal neurologic symptoms, which may be associated with headache, dizziness, nausea, and vomiting. Blood pressure is often elevated at presentation, and especially so with ICH. Patients with ICH often worsen over minutes to hours as clot expansion occurs.
- **SAH:** sudden severe headache with transient loss of consciousness and nausea/vomiting. Mental status may return to normal, or may stay impaired. Mental status may worsen if hydrocephalus develops.

Clinical diagnosis

History

- When was the patient last known to be well or time of onset of symptoms?
- What were the initial symptoms and signs?
- Review any vascular risk factors including diabetes.
- Prior history of seizures.
- Medications – anticoagulants and note time of last dose.
- Any medical history that might exclude thrombolytic therapy.
- Pre-morbid functional status.

Physical examination

- Neurologic exam:
  - Perform the NIH Stroke Scale (NIHSS).
  - Evaluate for signs of clinical seizures.
- Cardiovascular: evidence of arrhythmia, congestive heart failure, variance in pulses, bruits.
- Pulmonary: respiratory distress, neurogenic pulmonary edema, aspiration/inability to protect airway.

Stroke severity scales

The NIH Stroke Scale

Tested Item	Title	Responses and Scores
IA	Level of consciousness	0—Alert 1—Drowsy 2—Obtunded 3—Coma/unresponsive
1B	Orientation questions (2)	0—Answers both correctly 1—Answers 1 correctly 2—Answers neither correctly
1C	Response to commands (2)	0—Performs both tasks correctly 1—Performs 1 task correctly 2—Performs neither
2	Gaze	0—Normal horizontal movements 1—Partial gaze palsy 2—Complete gaze palsy
3	Visual fields	0—No visual field defect 1—Partial hemianopia 2—Complete hemianopia 3—Bilateral hemianopia
4	Facial movement	0—Normal 1—Minor facial weakness 2—Partial facial weakness 3—Complete unilateral palsy
5	Motor function (arm) a. Left b. Right	0—No drift 1—Drift before 5 seconds 2—Falls before 10 seconds 3—No effort against gravity 4—No movement

(*Continued*)

(*Continued*)

Tested Item	Title	Responses and Scores
6	Motor function (leg) a. Left b. Right	0—No drift 1—Drift before 5 seconds 2—Falls before 5 seconds 3—No effort against gravity 4—No movement
7	Limb ataxia	0—No ataxia 1—Ataxia in 1 limb 2—Ataxia in 2 limbs
8	Sensory	0—No sensory loss 1—Mild sensory loss 2—Severe sensory loss
9	Language	0—Normal 1—Mild aphasia 2—Severe aphasia 3—Mute or global aphasia
10	Articulation	0—Normal 1—Mild dysarthria 2—Severe dysarthria
11	Extinction or inattention	0—Absent 1—Mild (1 sensory modality lost) 2—Severe (2 modalities lost)

The ICH score

This predicts mortality at 30 days:

- GCS 3–4, 5–12, versus 13–15.
- Age > or = 80 years.
- Infratentorial ICH.
- Volume >30 mL.
- Presence of intraventricular blood.

SAH disease severity scores

- Hunt and Hess grade:
  - 1 – no or minimal headache, mild neck stiffness.
  - 2 – moderate–severe headache, neck stiffness, cranial nerve palsy.
  - 3 – drowsy, minimal neurologic deficit.
  - 4 – stupor, moderate–severe hemiparesis.
  - 5 – deep coma, decerebrate.

Laboratory diagnosis

List of diagnostic tests

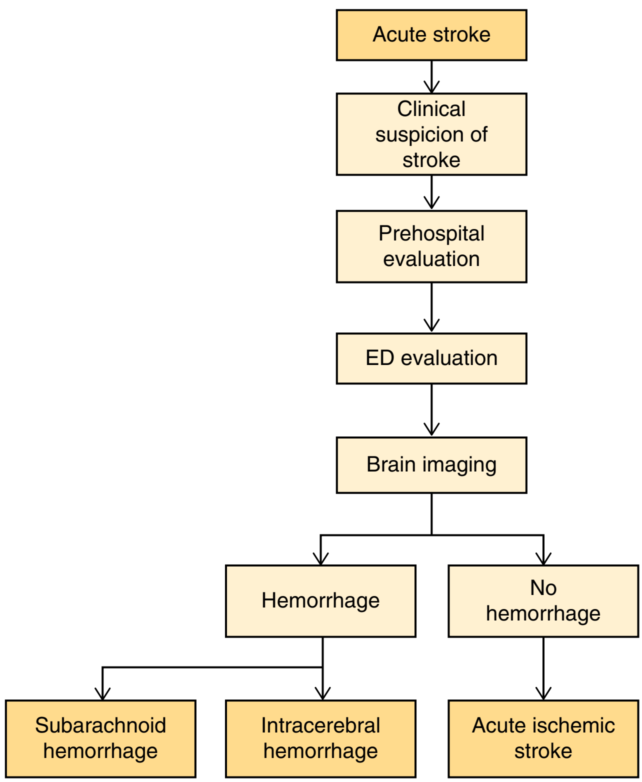
- Basic metabolic panel.
- CBC with platelet count.
- PT, INR, and PTT.
- Fingerstick glucose (note that this is the only test required before giving IV tissue plasminogen activator (tPA), unless a bleeding diathesis or liver failure is suspected, or if the patient is on warfarin).
- Lumbar puncture – in cases of suspected SAH with negative head CT scan.

List of imaging techniques

- Non-contrast CT head: rule out blood, early infarct signs.
- CT angiography head and neck: rapid scan done readily in the ER – evaluate for large vessel occlusion (LVO), 'spot sign,' or AVM with ICH, and cerebral aneurysm with SAH.
- CT perfusion: rapid scan done readily in the ER – identify potential clot retrieval candidates in the setting of unknown time of onset of ischemic stroke with LVO.
- MRI brain: can identify ischemic stroke, hemorrhage, and underlying lesions. In wake-up stroke patients, identification of a DWI lesion in the absence of a corresponding FLAIR lesion can be used to identify potential candidates for tPA outside of the conventional 3 hour window.
- MRA head and neck: consider special sequences for arterial dissection evaluation, and magnetic resonance venogram to evaluate for cerebral venous sinus thrombosis.

Diagnostic algorithm (Algorithm 27.1)

Algorithm 27.1 Diagnosis of acute stroke (Source: Emergency Neurological Life Support, Neurocritical Care Society)



Potential pitfalls/common errors made regarding diagnosis of disease

- Patients with large hemispheric stroke or basilar artery occlusion may present with shaking limbs and altered consciousness, leading to a misdiagnosis of seizure as the primary event.
- Atypical stroke symptoms, such as dizziness, difficulty walking without paralysis, a fluent aphasia appearing to the untrained eye as 'confusion,' and missed visual field loss or inattention have led to a delay in diagnosis.

Treatment

Treatment rationale

- Ischemic stroke:
  - Restore cerebral blood flow as quickly as possible in patients presenting acutely.
    - IV thrombolysis in patients presenting up to 4.5 hours from onset. Newer protocols allow for thromboysis for wake-up strokes that are DWI+ and FLAIR– on MRI.
    - Intra-arterial mechanical thrombectomy (Figure 27.4) (LVO identified) up to 6 hours from onset (up to 24 hours for significant penumbra on CT perfusion or for basilar artery occlusion).
- Hemorrhagic stroke:
  - Prevent clot expansion by controlling BP and reversing any coagulation defects.
  - Control ICP and cerebral edema.
- Subarachnoid hemorrhage:
  - Stabilize the patient regarding airway and BP control, with the goal to avoid re-rupture of the aneurysm.
  - Secure the aneurysm early.
  - Take measures to avoid symptomatic vasospasm once the aneurysm is secured.

When to hospitalize

- All patients with TIA (ABCD2 score >3), acute stroke, ICH, or SAH are hospitalized.
- TIA patients of low risk may be investigated as an outpatient (ABCD2 score ≤3 without another new indication, e.g. new atrial fibrillation).

Table of specific treatments for stroke

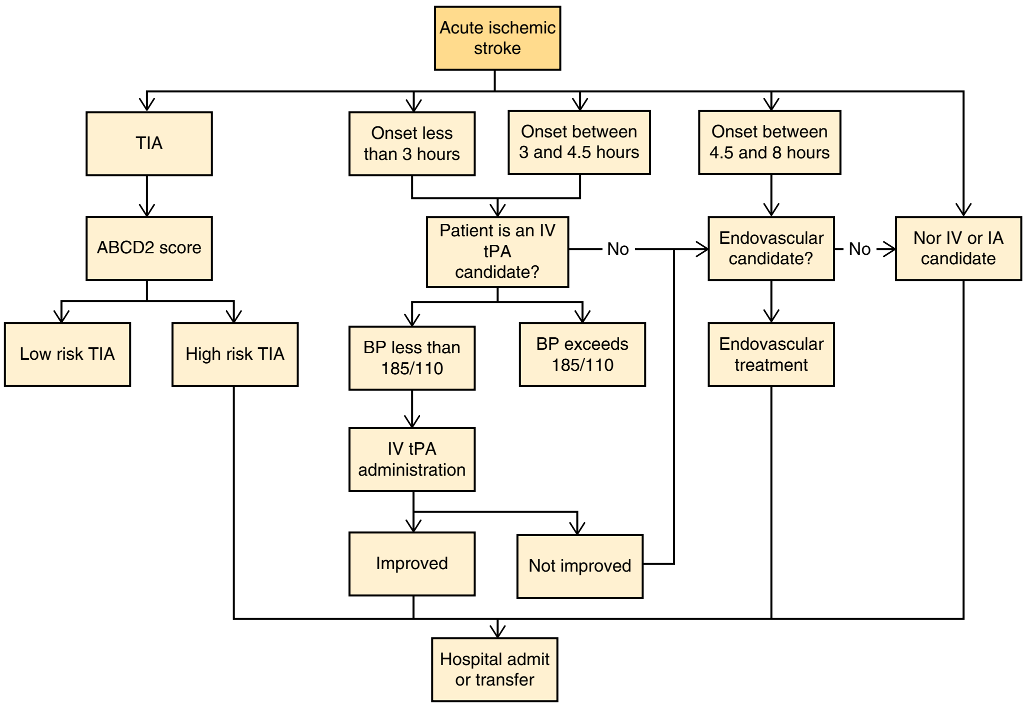
Treatment	Comments
Intravenous thrombolysis	Patient with acute stroke symptoms presenting within 3 hours of onset and with negative CT findings may be treated with IV tPA Patients presenting within 4.5 hours of onset with a negative CT scan and who are also of age <80, have an NIHSS <25, are not diabetic and have a prior history of stroke, and are not on anticoagulation may also be treated with IV tPA
Intra-arterial clot retrieval or thrombolysis	Patients with suspected ischemic stroke with evidence of an LVO on CT angiography may be treated with IA tPA within 6 hours and IA clot retrieval within 8 hours of symptom onset
Craniotomy for clot evacuation	Patients presenting with posterior fossa ICH of ≥3 cm should undergo posterior fossa decompression and evacuation of the hematoma Patients with superficial lobar ICH with mass effect may benefit from open craniotomy to evacuate the hematoma
Craniotomy/clipping of cerebral aneurysm	Ruptured cerebral aneurysms with a wide neck that are not amenable to endovascular coiling, or of MCA location, should be treated with clipping of the aneurysm
Endovascular coiling of cerebral aneurysm	Ruptured cerebral aneurysms with a narrow neck amenable to coiling, and aneurysms of the posterior fossa should be treated with endovascular coiling
Hypertonic saline or mannitol for control of cerebral edema and elevated ICP	Hyperosmolar therapy, along with other measures such as head elevation, CSF drainage, and sedation
Hemicraniectomy and durotomy for malignant hemispheric infarction or ICH	For cases of refractory malignant brain edema and raised ICP, hemicraniectomy can be considered to prevent brain herniation
Ventriculostomy placement, lumbar drainage, or serial lumbar punctures	Hydrocephalus as a result of ICH or SAH may be managed with continuous or intermittent CSF drainage, depending upon the circumstances and patient

Prevention/management of complications

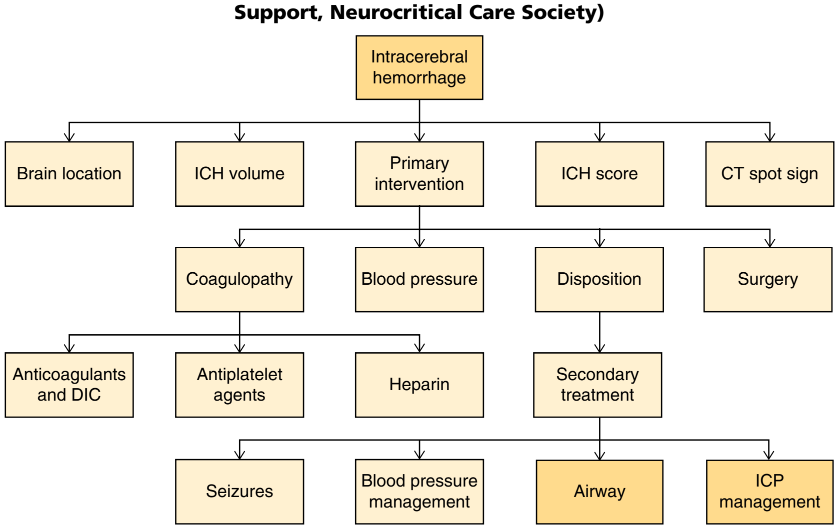
- Aspiration pneumonia: dysphagia screening and aspiration precautions are required.
- Deep venous thrombosis: subcutaneous unfractionated or low molecular weight heparin should be initiated within 24 hours of acute stroke.

Management/treatment algorithms (Algorithms 27.2–27.4)

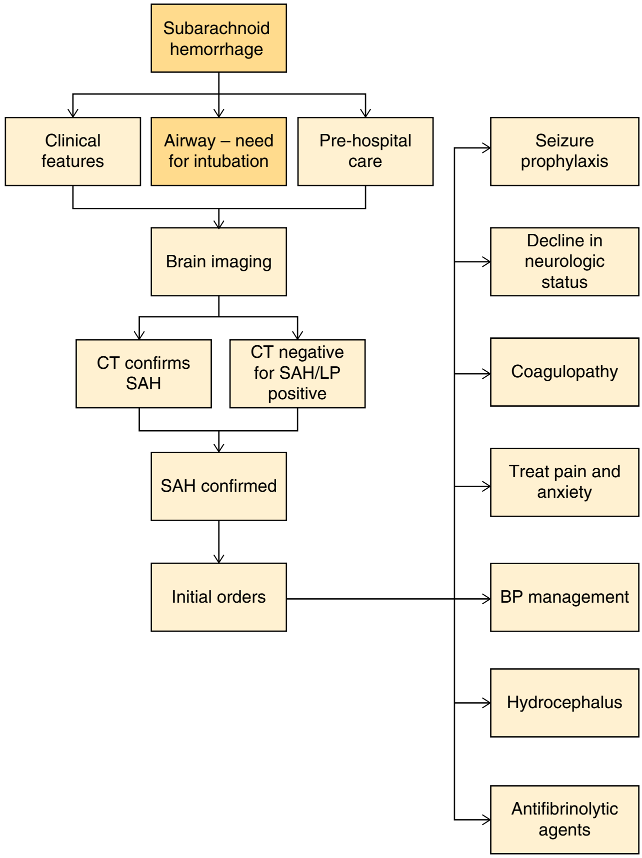
Algorithm 27.2 Management of acute ischemic stroke (Source: Emergency Neurological Life Support, Neurocritical Care Society)



Algorithm 27.3 Management of intracerebral hemorrhage (Source: Emergency Neurological Life Support, Neurocritical Care Society)



Algorithm 27.4 **Management of subarachnoid hemorrhage (Source: Emergency Neurological Life Support, Neurocritical Care Society)**



Special populations

Pregnancy

Intravenous thrombolysis with alteplase (tPA) – category C. Alteplase is only recommended for use during pregnancy when benefit outweighs risk.

Elderly

Age >80 years is a contraindication to treating acute stroke within 3–4.5 hours from onset of symptoms with IV tPA.

Prognosis

BOTTOM LINE

- In ischemic stroke with LCO, re-canalization is associated with improved outcome and lower mortality.
- Re-canalization rate with IV tPA alone is ~40%, whereas re-canalization rates of up to 88% have been achieved with the newer stent retrieval devices.
- With all forms of AIS treatment, better outcome is achieved with faster treatment times.

Natural history of untreated disease

- Strongest predictors of poor outcome with acute ischemic stroke include stroke severity and patient age.
- Mortality of 21% at 90 days was noted in the placebo arm of the 1995 NINDS tPA Trial.
- An estimated 15–30% of patients with aneurysmal SAH die before reaching the hospital.

Prognosis for treated patients

A recent meta-analysis of nine RCTs of IV tPA for AIS demonstrated benefit of better outcome with IV tPA versus placebo with an OR of 1.75, and a recent meta-analysis of five tPA ± IA thrombectomy trials revealed that earlier treatment with combined tPA/thrombectomy resulted in lower degrees of disability at 3 months.

Follow-up tests and monitoring

Serial carotid duplex, MRA, or CT angiography imaging may be warranted in the case of atherosclerotic large vessel disease and arterial dissection.

Reading list

American College of Emergency Physicians; American Academy of Neurology. Clinical policy: use of intravenous tPA for the management of acute ischemic stroke in the emergency department. Ann Emerg Med 2013; 61:225–43.

Demaerschalk BM, et al. Scientific rationale for the inclusion and exclusion criteria for IV alteplase in acute ischemic stroke (AHA/ASA scientific statement). Stroke 2016;47:581–641.

Lee KH, Lukovits T, Friedman JA. 'Triple-H' therapy for cerebral vasospasm following subarachnoid hemorrhage (review). Neurocrit Care 2006;4:68–76.

Mendelow D, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobal intracerebral haematomas (STICH II): a randomized trial. Lancet 2013;382:397–408.

Sacco RL, et al. An updated definition of stroke for the 21st century (AHA/ASA Expert Consensus document). Stroke 2013;44:2064–89.

Saposnik G, et al. Diagnosis and management of cerebral venous thrombosis (AHA/ASA scientific statement). Stroke 2011;42:1158–92.

Vespa PM, et al. Surgical trials in intracerebral hemorrhage. Stroke 2013;44:S79–82.

Suggested websites

www.neurocriticalcare.org
www.snisonline.org
www.stroke.aha.journals.org

Guidelines

National society guidelines

Title	Source	Date and reference
Guidelines for the Primary Prevention of Stroke	American Heart Association (AHA)/ American Society of Anesthiologists (ASA)	2014 Stroke 2014;45:3754–832
Guidelines for the Prevention of Stroke in Patients with Stroke and TIA	AHA/ASA	2014 Stroke 2014;45:2160–236
Guidelines for the Early Management of Patients with Acute Ischemic Stroke	AHA/ASA	2013 Stroke. 2013;44:870–947

(*Continued*)

(*Continued*)

Title	Source	Date and reference
2015 AHA/ASA Focused Update of the 2013 Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment	AHA/ASA	2015 Stroke 2015;46:3024–39
Guidelines for the Management of Spontaneous Intracerebral Hemorrhage	AHA/ASA	2015 Stroke 2015;46:1–29
Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage	AHA/ASA	2012 Stroke 2012;43:1711–37
Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference	Neurocritical Care Society (NCS)	2011 Neurocrit Care 2011;15:211–40
Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling	AHA/ASA	2014 Stroke 2014;45:1222–38
Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage	NCS and Society of Critical Care Medicine (SCCM)	2016 Neurocrit Care 2016;24:6–46
Evidence-Based Guidelines for the Management of Large Hemispheric Infarction	NCS	2015 Neurocrit Care 2015;22:146–64

Evidence

Type of evidence	Title	Date and reference
RCT	*Tissue Plasminogen Activator for Acute Ischemic Stroke (NINDS and Stroke rt-PA Stroke Study Group)*	1995 N Engl J Med 1995;333:1581–8
Meta-analysis	*Effect of Treatment Delay, Age, and Stroke Severity on the Effects of IV Thrombolysis With Alteplase for Acute Ischaemic Stroke: A Meta-Analysis of Individual Patient Data from Randomized Trials*	2014 Lancet 214;384:1929—5
Meta-analysis	*Time to Treatment With Endovascular Thrombectomy and Outcomes from Ischemic Stroke: A Meta-analysis*	2016 JAMA 2016;316(12):1279–88
Meta-analysis	*Endovascular Treatment Versus Medical Care Alone for Ischaemic Stroke: A Systemic Review and Meta-Analysis*	2016 BMJ 216;353:i1754
RCT	*Rapid Blood-Pressure Lowering with Acute Intracerebral Hemorrhage (INTERACT 2 Trial)*	2013 N Engl J Med 2013;368:2355–65
RCT	*Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage (ATACH-2 Trial)*	2016 N Engl J Med 2016;375:1033–43
Review of RCT and meta-analysis	*Vasospasm After Aneurysmal Subarachnoid Hemorrhage: Review of RCTs and Meta-Analysis in the Literature*	2011 World Surg 2011;76(5):446–54

Images

(A) (B)

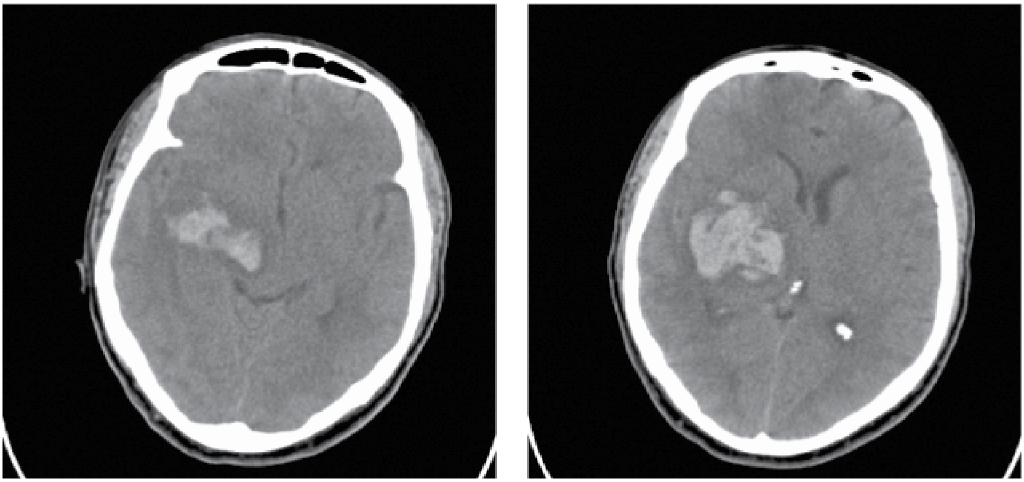


Figure 27.1 (A,B) Typical hypertension-related basal ganglia/thalamic ICH.

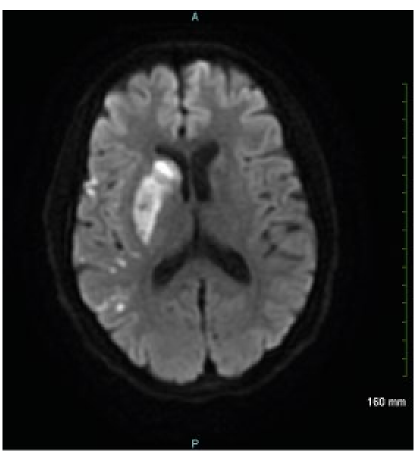


Figure 27.2 MRI FLAIR image demonstrating a right striatocapsular infarct involving the caudate and globus pallidus. Speckled foci of infarction are also visible in the overlying cortex.

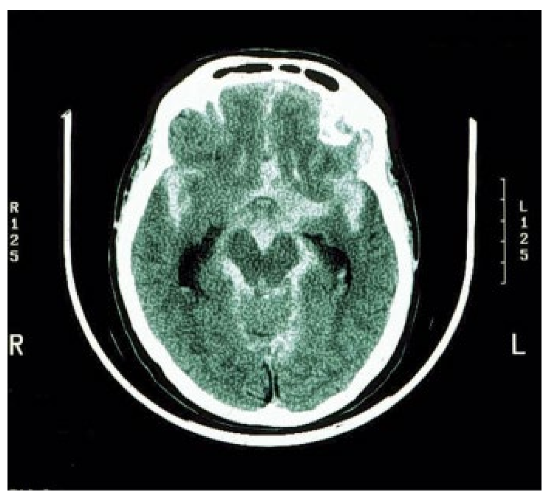


Figure 27.3 Subarachnoid hemorrhage with enlargement of the temporal horns of the lateral ventricles (hydrocephalus).

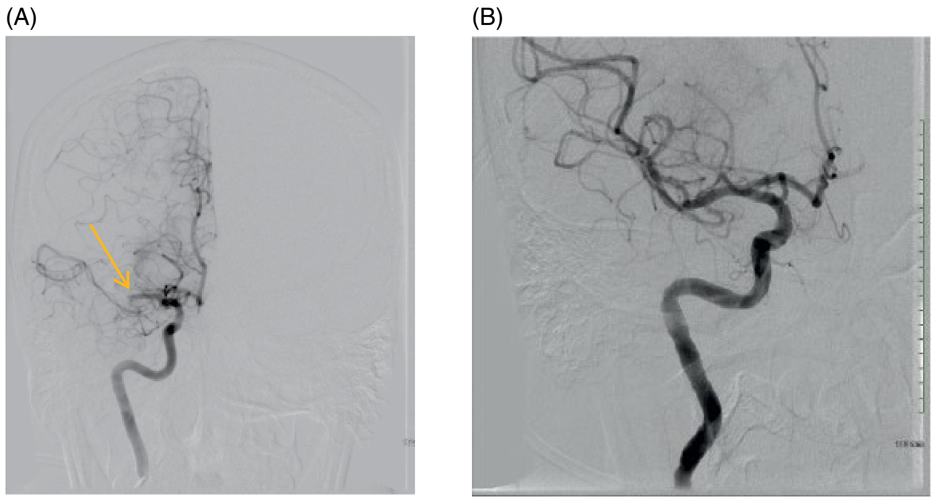


Figure 27.4. (A) Occlusion of the right middle cerebral artery (MCA) due to thromboembolism (yellow arrow). (B) Recanalization of the MCA after mechanical thrombectomy.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions and case study.

CHAPTER 28

Neurotrauma

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OVERALL BOTTOM LINE

- Neurotrauma comprises a diverse spectrum of traumatic CNS injuries, including traumatic brain injury (TBI) and spinal cord injury (SCI).
- Prompt recognition and transport of neurotrauma patients to definitive care for medical/surgical management is paramount to prevent secondary neurologic injury.
- Maintenance of CNS tissue perfusion/oxygenation is key to preventing secondary injury and maximizing good outcomes.
- Patients suspected of blunt spine injuries should have the spine immobilized initially with a rigid cervical collar and backboard to prevent secondary injuries from mechanical instability.
- Emergency neurosurgical management of TBI and SCI may be required. Guidelines-based neurotrauma management has been shown to improve outcomes.

Background

Definition of disease

- Traumatic injuries of the CNS (brain/spinal cord) are caused by external forces.
- External forces include blunt (e.g. direct impact, acceleration/deceleration, blast wave) and penetrating (e.g. shrapnel, stab, gunshot wound) injuries.

Disease classification

- TBI is classified according to severity using the GCS, into mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS 3–8) TBI (see Chapter 31, Coma). It may also be classified according to injury mechanism (e.g. blunt, penetrating), injury pathoanatomy (e.g. skull fracture, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, contusion, diffuse axonal injury), or radiographic characteristics (e.g. Marshall CT scale).
- SCI is classified according to neurologic level of injury (i.e. cervical, thoracic) and severity using the American Spinal Injury Association (ASIA) impairment scale, ranging from grade A (complete SCI with no motor/sensory function preserved below the injured level) to grade E (complete recovery of neurologic function).

Incidence/prevalence

- Approximately 2.5 million people sustain a TBI each year in the USA, the majority (~75%) are concussions/mild TBI, with the remainder either moderate or severe TBI (sTBI).

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- More than 280 000 patients are hospitalized and >50 000 patients die from TBI annually in the USA; >5.3 million people in the USA are living with permanent disability from TBI.
- The annual incidence of SCI is 54 cases/million population (~17 000 cases/year) and ~280 000 persons are living with sequelae from SCI in the USA.

Etiology

- Most TBIs are blunt injuries, commonly falls, followed by motor vehicle accidents (MVAs), colliding with/struck by an object, and assaults.
- Penetrating brain injury (e.g. stab/gunshot) is less common.
- Leading causes of SCI are MVAs, followed by falls, violence (e.g. gunshot), and sports-related.

Pathology/pathogenesis

- Primary injury to CNS tissue occurs during the initial impact, resulting in direct brain or spinal cord damage, such as contusion, laceration, hemorrhage, or compression.
- Following primary injury, a cascade of pathophysiologic events is initiated that can lead to secondary brain or spinal cord injury.
- The main mechanism of secondary injury is ischemia, resulting from hypoperfusion (hypotension), hypoxia (hypoxemia), increased and unmet metabolic demands (seizures, fevers), or ongoing compression (non-evacuated hematoma or unreduced spine injury).
- Cerebral blood flow (CBF) is defined as cerebral perfusion pressure (CPP) divided by cerebrovascular resistance (CVR): CBF = CPP/CVR.
- CPP is defined as mean arterial pressure (MAP) minus intracranial pressure (ICP): CPP = MAP – ICP.
- Factors that reduce MAP (e.g. hemorrhagic or neurogenic shock, hypovolemia, medications) can impair brain or spinal cord perfusion.
- Factors that increase ICP (cerebral vasodilation from hypercapnia, decreased venous return, intracranial hematomas, cerebral edema, hydrocephalus, seizures) or increase CVR (cerebral vasoconstriction from hypocapnia, traumatic vasospasm) also impair brain perfusion.
- In the uninjured brain, cerebral autoregulation maintains a constant CBF over a range of MAPs, protecting cerebral tissue from hypoperfusion; however, cerebral autoregulation is frequently impaired following TBI, resulting in CBF being pressure dependent.
- Impaired cerebral autoregulation following TBI places cerebral tissue at increased risk of hypoperfusion and secondary ischemic injury.
- Cerebral hypoxia due to ventilation-related issues may lead to cerebral ischemia and secondary injury.
- Following SCI there is the possibility of ‘repeat’ primary injury, wherein insufficient spine immobilization in the setting of an unstable spine can result in additional primary injury.

Predictive/risk factors

- Male gender.
- Adolescence/young adulthood.
- Elderly (age ≥65 years).
- High energy mechanism.
- Risky behavior (e.g. not wearing a helmet.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Use of seatbelts/airbags in motor vehicles, helmets for motor/bicyclists/sports, along with public education aimed at increasing awareness.
- Fall prevention strategies and equipment in elderly adults.

Screening

- Patients with altered mental status or a neurologic deficit following a traumatic injury should be screened for TBI or SCI.
- Patients who are elderly, on anticoagulant/antiplatelet medications, intoxicated, have pre-existing spine disease (e.g. cervical stenosis, ankylosing spondylitis), or a high energy mechanism of injury, are at increased risk of neurotrauma.

Primary prevention

- Protective equipment (seatbelts, airbags, helmets) can reduce the likelihood of neurotrauma following MVAs and sports-related events.
- Fall prevention strategies/equipment can reduce the risk of neurotrauma in the elderly.
- Secure storage of firearms can reduce accidental injuries.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- History of trauma with loss of consciousness (LOC) or altered mental status is a red flag for an important new neurologic deficit.
- History of anticoagulation or antiplatelet medication use should always be identified and reversed if there is any sign of intracranial bleeding.
- Serial neurologic exams with focus on level of consciousness (GCS), brainstem reflexes, and motor examination are paramount.
- Consider MRI if the extent of neurological deficit is unexplained by CT.

Differential diagnosis of traumatic intracranial hemorrhage

Differential diagnosis	Features
Spontaneous ICH	No known trauma, witnessed syncopal event preceding fall, history of hypertension, lobar or predominantly basal ganglia location of ICH, vascular lesion (aneurysm, arteriovenous malformation) on CT angiography
Aneurysmal SAH	No known trauma, classic 'thunderclap' headache, prior 'sentinel' headaches, basal cistern > cortical SAH, aneurysm on CT angiography
Transverse myelitis	No known trauma, progressive neurologic deficit over hours/days, no mechanical spine injury on CT or MRI

Typical presentation

- Patients typically present with LOC, altered mental status, or a neurologic deficit following neurotrauma.
- Moderate/severe TBI often results in transient or permanent LOC.
- Patients may be apneic after TBI or high cervical SCI.
- Ictal or early seizures are not uncommon with TBI.
- Flexor (decorticate) or extensor (decerebrate) posturing may be seen after TBI.
- Unilateral/bilateral, fixed, and dilated pupils often signifies ongoing cerebral herniation.
- Patients with incomplete SCI present with motor weakness and varying degrees of preserved sensation below the neurologic level of injury. Those with complete SCI have no motor/sensory function below the level of injury.

Clinical diagnosis

History

- Mechanism of injury helps determine the force/energy involved and often correlates with severity and potential for associated injuries.
- Specific circumstances of the injury help distinguish from primary versus secondary traumatic injury (e.g. seizure from spontaneous ICH leading to secondary TBI).
- Time between injury and arrival to the ED, total time elapsed since injury.
- LOC, presence of retrograde or post-traumatic amnesia.
- Episodes of hypotension/hypoxia in the field or in the ED.
- Progressive neurologic deficit, suggesting worsening pathology (e.g. expanding epidural hematoma).
- Any confounders that may be affecting assessment of the neurologic exam (drugs, alcohol, medications such as sedatives, analgesia, paralytics).
- Ictal/early post-traumatic seizures.
- Medications/conditions that may affect coagulation/platelet function.

Physical examination

- Assessment of airway, breathing, circulation, and primary survey per American College of Surgeons (ACS) advanced traumatic life support (ATLS) protocols.
- Level of consciousness (GCS score).
- Pupillary exam, including size, shape, and response to light.
- Motor response in all extremities; in obtunded/comatose patients, assess via central noxious stimulus (e.g. supraorbital, sternal, or trapezius pressure) as well as peripheral stimulus to limbs.
- Detailed motor/sensory exam for SCI to determine the motor, sensory, and neurologic levels of injury, and assign ASIA grade to injury.
- Evaluate for external signs of trauma: scalp lacerations or open/closed skull fractures; rhinorrhea/otorrhea, periorbital bruising ('raccoon eyes'), or bruising over the mastoid process ('Battle's sign') suggest skull base fracture; spine step deformities suggest fracture or subluxation; extremity fractures/injuries may confound neurologic exam.

Useful clinical decision rules and calculators

- Glasgow Coma Scale (GCS).
- Canadian CT Head Rule.
- NEXUS Low-Risk Criteria for cervical spine injury.
- Canadian Cervical Spine Rule.
- Subaxial Cervical Spine Injury Classification (SLIC) system.
- Thoracolumbar Injury Classification and Severity (TLICS) scale.

Disease severity classification

- TBI severity is most commonly assessed using post-resuscitation GCS score, the sum of the patient's best eye, verbal, and motor responses, producing a score from 3 (worst) to 15 (best).
- SCI severity is assessed by determining the post-resuscitation neurologic level of injury and the ASIA Impairment Scale grade, ranging from grade A (complete SCI with no motor/sensory function below neurologic level of injury) to grade E (complete recovery of neurologic deficits).

Laboratory diagnosis

List of diagnostic tests

- CBC with emphasis on hemoglobin level and platelet count.
- Metabolic panel with emphasis on serum sodium level.
- Coagulation studies (PT/INR, PTT).
- Consider platelet function assays if history of antiplatelet medications or unexplained bleeding diathesis.

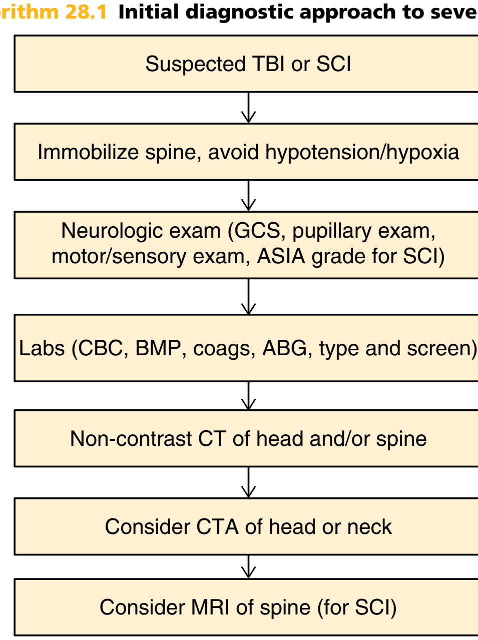
- Arterial blood gas analysis (PaO_2, $PaCO_2$).
- Blood type and screen, as transfusion of blood products may be necessary.
- Beta-2 transferrin, in the setting of rhinorrhea/otorrhea, to confirm CSF leak from skull base fracture.

List of imaging techniques

- Non-contrast head CT in patients with suspected TBI to identify intracranial hemorrhage, edema, mass effect, and skull fractures. Indicated for patients with GCS <13 (i.e. moderate/severe TBI) on presentation or GCS <15 at 2 hours post-injury, suspected skull base or open/depressed skull fracture, two or more vomiting episodes, age ≥65 years, retrograde amnesia ≥30 minutes, or dangerous mechanism of injury (e.g. fall >1 m or >5 stairs, ejected from vehicle, pedestrian hit by car).
- Follow-up non-contrast head CT within 6 hours if initial CT was abnormal. Repeat scans until intracranial abnormalities are stable (i.e. no further hematoma expansion) or for clinical deterioration (worsened GCS ≥2 points).
- CTC of the head is indicated to rule out cerebrovascular injury in the presence of skull base fracture involving the carotid canal, LeFort type 2/3 and mandible fracture, Horner's syndrome, diffuse axonal injury with GCS <6, penetrating brain injury, or neurologic exam incongruous with non-contrast head CT.
- Brain MRI without contrast is an option for stabilized patients without ICP crisis to evaluate for diffuse axonal injury. MRI is a follow-up study option in pediatric patients to avoid excessive exposure to ionizing radiation.
- Non-contrast spine CT is indicated in trauma patients with spine pain/tenderness, radiculopathy, step deformity, or motor/sensory deficit. In obtunded/comatose trauma patients there should be a low threshold to obtain a CT to rule out spine trauma.
- CTA of the neck is indicated for C1–C3 and transverse foramen fractures or cervical spine subluxation to rule out vertebral artery injury.
- Spine MRI without contrast can provide useful information when a neurologic deficit cannot be adequately explained by CT findings (e.g. traumatic disc herniation), or for preoperative planning and decision making (assessment of ligamentous injury).

Diagnostic algorithm (Algorithm 28.1)

Algorithm 28.1 Initial diagnostic approach to severe TBI



Potential pitfalls/common errors made regarding diagnosis of disease

- Following TBI, a hematoma may cause compression of the contralateral cerebral peduncle against the tentorial incisura resulting in ipsilateral, rather than contralateral, weakness ('Kernohan's notch' phenomenon).
- A fixed and dilated pupil is usually ipsilateral to an intracranial hematoma causing herniation.

Treatment

Treatment rationale

- Initial treatment is aimed at resuscitation and maintaining the airway, breathing, and circulation.
- Avoidance and rapid correction of hypotension/hypoxia is of paramount importance during the acute phase after neurotrauma to avoid secondary injury.
- Spine immobilization should be performed if there is suspicion for spine injuries.
- Normocapnea should be maintained, as hypocapnia (i.e. excessive hyperventilation) results in cerebral vasoconstriction and decreased CBF, whereas hypercapnia leads to vasodilation and elevated ICP.
- In comatose patients with ICP should be monitored and treatment initiated if there is evidence of intracranial hypertension.
- Steroid administration is not recommended following TBI and is controversial after SCI.
- Normothermia should be maintained as fevers are associated with worse outcomes following TBI. Prophylactic hypothermia is not recommended.
- Prophylactic AEDs reduce the incidence of early post-traumatic seizures following TBI. Seizures should be rapidly treated as they increase cerebral metabolic demands.
- Surgical intervention should be considered in patients following TBI with large extra-axial hematomas, midline shift, basal cistern effacement, depressed skull fractures, deteriorating neurologic status, or elevated ICP refractory to medical management.
- Surgical intervention should be considered in patients following SCI who require spinal cord decompression and spine stabilization.

When to hospitalize

- GCS <15 (ICU if GCS <14 or hemodynamic instability).
- New neurologic deficit.
- Open, comminuted, or depressed skull fracture.
- Intracranial hemorrhage.
- Unstable spine fracture.
- Spinal cord compression.

Table of treatment

Treatment	Comments	
Medical management	TBI: SBP ≥110 mmHg SCI: MAP 85–90 mmHg ICP ≤22 mmHg CPP ≥60 mmHg SpO_2 ≥95% PaO_2 ≥100 mmHg $PaCO_2$ 35–45 mmHg	Platelets ≥75 × $10^3/mm^3$ Serum Na 135–145 mEq/L INR ≤1.4 Temperature 36–38°C Hemoglobin ≥7 g/dL pH 7.35–7.45 Blood glucose 80–180 mg/dL
Seizure prophylaxis	AEDs for 7 days following sTBI	
DVT prophylaxis	Pharmacologic prophylaxis (LDUH or LMWH) within 72 hours of injury if imaging is stable	

(*Continued*)

Treatment	Comments
Nutrition	Begin post-pyloric feeding to attain basal caloric requirements by 5–7 days post-injury at the latest
Tracheostomy	Consider earlier tracheostomy in patients with sTBI or high-cervical SCI likely to require prolonged ventilation
Steroids	Steroids increase mortality following sTBI Use is controversial following SCI
ICP monitoring indications	Salvageable patients with GCS ≤8 and abnormal head CT or normal head CT with ≥2 of the following on admission: age >40 years, unilateral/bilateral motor posturing, SBP <90 mmHg
Management of elevated ICP (tier 1)	Elevate head of bed to 30° Cervical spine in neutral position, minimize venous outflow obstruction Sedation/analgesia with short-acting agents Ventricular CSF drainage Consider repeat CT if tier 1 methods fail to control ICP, proceed rapidly to tier 2
Management of elevated ICP (tier 2)	If using parenchymal ICP monitor, consider placing external ventricular drain Hyperosmolar therapy with intermittent boluses of mannitol 0.25–1 g/kg body weight or hypertonic saline (e.g. 250 mL 3% or 30 mL 23.4%) every 4–6 hours Mild hyperventilation ($PaCO_2$ 30–35 mmHg) in presence of adequate neuromonitoring ($PbtO_2$, $SvjO_2$, CBF) to avoid brain hypoxia Test dose of neuromuscular-blocking agent
Management of elevated ICP (tier 3)	Continuous infusion of neuromuscular-blocking agent Barbiturate/propofol coma Mild hypothermia (<36°C) Decompressive craniectomy
Surgical management of TBI	Epidural hematoma >30 cm^3, >15 mm thickness, >5 mm midline shift, or focal deficits Subdural hematoma >10 mm thickness, >5 mm midline shift, or comatose patient with GCS decline ≥2 points, or pupillary abnormalities Intraparenchymal traumatic hematoma (contusion) with refractory intracranial hypertension, >5 mm midline shift, or cisternal compression Posterior fossa hematoma causing neurologic dysfunction or significant mass effect on fourth ventricle Cranial fractures depressed more than skull thickness Open cranial fractures, especially if frontal sinus involvement, dural penetration, significant intracranial hematoma, or gross wound contamination
Surgical management of SCI	For persistent malalignment with spinal cord compression, closed/open reduction with/without decompression as soon as hemodynamically stable Definitive spine stabilization after SCI is often achieved by instrumentation

Prevention/management of complications

- If intubation is necessary, perform rapid sequence intubation using short-acting agents that cause minimal decrease in blood pressure to avoid iatrogenic hypotension and secondary injury.
- Minimize neck manipulation/extension when cervical injury is suspected.
- Preference for hypertonic saline over mannitol in hypovolemic/hypotensive patients to avoid worsening cerebral perfusion.

Management/treatment algorithms (Algorithms 28.2 and 28.3)

Algorithm 28.2 Management/treatment algorithm for TBI

Assess GCS, neurologic exam

↓

Avoid hypotension/hypoxia, immobilize spine, prophylactic AEDs, optimize coagulation status

↓

If imminent herniation, temporize with hyperosmolar therapy and brief hyperventilation

↓

± Emergent craniotomy/craniectomy

↓

± ICP monitor placement (external ventricular drain, parenchymal ICP monitor) if GCS ≤8 and abnormal CT

↓

Management of elevated ICP (tier 1); proceed to tier 2 therapies if ICP >22 mmHg

↓

Management of elevated ICP (tier 2); consider repeat CT; proceed to tier 3 therapies if ICP >22 mmHg

↓

Management of elevated ICP (tier 3); consider repeat CT

Algorithm 28.3 Management/treatment algorithm for SCI

Avoid hypotension/hypoxia, MAP 85–90 mmHg for 7 days, immobilize spine

↓

Immediate decompression (closed or open reduction) if spinal cord compression

↓

Definitive stabilization (often surgically)

↓

Antiplatelet or anticoagulation medications for concomitant vertebral artery injury

CLINICAL PEARLS

- Following sTBI, maintain SBP ≥100–110 mmHg, CPP ≥60 mmHg, normocapnea, normothermia, normonatremia, monitor/treat elevated ICP, and promptly evacuate surgical mass lesions.
- Following SCI, maintain spine immobilization, maintain MAP 85–90 mmHg for 7 days post-injury, promptly decompress the spinal cord, and stabilize the spine as necessary.
- SCI above a T6 level may result in neurogenic shock refractory to fluid resuscitation due to loss of sympathetic outflow.
- Intubated SCI patients may require higher tidal volumes given paralysis of the diaphragm and intercostal muscles.

Special populations

Pregnancy

- Reduce mannitol bolus dose (0.25–0.5 mg/kg body weight) to avoid risk of fetal dehydration.
- Levetiracetam for seizure prophylaxis appears to be low risk for teratogenesis.

Children

- A modified GCS is used for young children to account for their non-verbal baseline.
- Infants have an open anterior fontanelle that allows for ICP estimation via direct palpation.
- Lower CPP thresholds are used for pediatric patients following TBI (≥40 mmHg for infants, ≥50 mmHg for adolescents).
- Prolonged propofol use is not recommended given the increased risk of propofol infusion syndrome.
- Consider non-accidental trauma for children presenting with TBI or spine injuries.

Elderly

- Intracranial hematomas may occur with relatively trivial trauma, given the increased incidence of antiplatelet/anticoagulant use in this age group.
- Intracranial hematomas may be quite large before causing symptoms associated with elevated ICP due to significant age-related cortical atrophy.

Others

- TBI patients with intracranial hemorrhage and a history of antiplatelet/anticoagulant use should undergo emergent reversal of these agents to prevent hemorrhage expansion and neurologic deterioration.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Age, post-resuscitation GCS score, and pupillary exam are the strongest prognostic variables following TBI.
- ASIA grade following SCI is an important prognostic indicator regarding future neurologic recovery.
- Hypotension and hypoxia are important modifiable predictors of outcome in neurotrauma.
- Rehabilitation is essential to optimize patient outcomes.

Natural history of untreated disease

- Severe TBI and SCI have extremely poor outcomes when not managed according to modern guidelines.
- Mortality from severe TBI has decreased from ~80% in the 1940s to <20% currently.

Prognosis for treated patients

- Prognostic calculators for TBI are available online:
  - IMPACT: http://www.tbi-impact.org/?p=impact/calc.
  - MRC CRASH: http://www.trialscoordinatingcentre.lshtm.ac.uk/Risk%20calculator/index.html.

Follow-up tests and monitoring

- Neurotrauma survivors require extensive rehabilitation to optimize outcomes.
- Survivors require prolonged follow-up given the potential for delayed complications (e.g. hydrocephalus, dysautonomia, infection, spasticity, syringomyelia, bowel/bladder dysfunction, pseudarthrosis, psychiatric sequelae).

Reading list

Barthelemy EJ, et al. Decompressive craniectomy for severe traumatic brain injury: a systematic review. World Neurosurg 2016;88:411–20.

Chesnut RM, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34(2):216–22.

Chesnut RM, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 2012;367(26):2471–81.
Fehlings MG, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One 2012;7(2):e32037.
Hutchinson PJ, et al.; RESCUEicp Trial Collaborators. Trial of decompressive craniectomy for traumatic intracranial hypertension. N Engl J Med 2016;375(12):1119–30.
Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81–4.

Suggested websites

www.asia-spinalinjury.org
www.braintrauma.org
www.neurotraumasection.org

Guidelines

National society guidelines

Title	Source	Date and weblink
Guidelines for the Management of Severe TBI, 4th edition	Brain Trauma Foundation, endorsed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons	2016 https://braintrauma.org/uploads/03/12/
Guidelines for the Acute Medical Management of Severe TBI in Infants, Children, and Adolescents, 2nd Edition	Brain Trauma Foundation, endorsed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons	2012 https://www.braintrauma.org/coma/guidelines

Evidence

Type of evidence	Comment	Date and reference
RCT	Increased mortality at 2 weeks in steroid group	2004 Roberts I, et al. *Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial.* Lancet 2004;364:1321–8
RCT	Increased mortality at 6 months in steroid group	2005 Edwards P, et al. *Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months.* Lancet 2005;365:1957–9

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 29

Status Epilepticus

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OVERALL BOTTOM LINE

- Status epilepticus is a neurologic and medical emergency and should be recognized and treated as soon as possible.
- In the critically ill population, the majority (~75%) of the seizures are non-convulsive and cannot be recognized without an EEG.
- Early recognition of status epilepticus and rapid treatment is necessary to prevent seizures from becoming refractory.
- Attention to medical complications, avoiding overtreatment, and considering the ultimate prognosis of individual patient is also necessary.

Background

Definition of disease

- Convulsive status epilepticus (CSE) is defined as 'an acute epileptic condition characterized by continuous generalized convulsive seizures for at least 5 minutes, or by 2 seizures without full recovery of consciousness between seizures.'
- Non-convulsive status epilepticus (NCSE) is defined as 'continuous or intermittent ictal discharges without the patient regaining consciousness, and no overt clinical signs of convulsive activity.'

Incidence/prevalence

- Between 20 and 40/100 000 per year in the USA, with a first peak before 1 year of age and a second peak after 60 years of age.
- About 31–43% of status epilepticus become refractory.
- NCSE affects up to 10% of patients with altered mental status and 16% of confused elderly patients.

Etiology

Common etiologies include anoxic brain injury, antibody-mediated disease (autoimmune or paraneoplastic), brain tumor, infection (meningitis, encephalitis, abscess, sepsis), drug or alcohol intoxication/withdrawal, low antiepileptic drug levels or change in antiepileptic drug regimen, metabolic disturbance, stroke, trauma, congenital malformation/remote brain injury, and idiopathic causes.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Pathology/pathogenesis

Status epilepticus occurs when there is either excessive excitation or ineffective inhibition of seizures. Increased excitation occurs as a result of increased glutamate or other excitatory amino acids. During status epilepticus, *N*-methyl-D-aspartate (NMDA) receptors accumulate rapidly and increase glutaminergic excitation. Decreased inhibition results from decreased γ-aminobutyric acid (GABA), and GABA-A receptors change in number and sensitivity during status epilepticus. Other mechanisms, such as mitochondrial failure, inflammatory processes, and changes in gene expression, are also involved.

Predictive/risk factors

Risk factor	Odds ratio
Coma	7.7
History of epilepsy	2.7
Convulsive seizures during the current illness prior to monitoring	2.4

Prevention

BOTTOM LINE/CLINICAL PEARLS
- Early diagnosis and initiation of treatment is crucial in the treatment of status epilepticus and prevention of refractory status epilepticus.
- The majority of seizures that occur in critically ill patients are non-convulsive seizures (~75%) and cannot be recognized without EEG.

Screening

- EEGs should be performed in:
  - Patients who are critically ill and have alteration of consciousness without an alternative explanation.
  - Patients who had convulsive seizures and did not return to their baseline within 10–20 minutes after cessation of convulsive activity.
  - Patients with unexplained focal neurologic deficits, such as hemiparesis, aphasia, or visual field defect.
  - Patients with repetitive, involuntary movements.
  - A 30–60 minute EEG monitoring will miss all seizures in more than half of patients having non-convulsive seizures.
  - Continuous monitoring is recommended for at least 24 hours for patients who are not comatose, and 48 hours for patients who are comatose or those with frequent periodic epileptiform discharges.

Diagnosis

- A careful history should be taken to investigate the etiology of the status epilepticus.
- Overt CSE is readily diagnosed by clinical presentation, and in this case, does not require continuous EEG.
- NCSE cannot be diagnosed without an EEG. In critically ill patients with decreased level of consciousness, regardless of primary neurologic or medical condition, NCSE is common. Patients with a history of epilepsy, fluctuating level of consciousness, acute brain injury, and recent CSE are at most risk for NCSE.
- ICU patients commonly have abnormal involuntary movements, which may not be epileptic in origin. Continuous EEG is indicated to correctly diagnose them in order to avoid unnecessary treatments.

UNIFIED EEG CRITERIA FOR NCSE

- Epileptiform discharges >2.5 Hz, *OR*
- Epileptifrom discharges ≤2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) *AND* one of the following:
  - EEG and clinical improvement after IV AED, *OR*
  - Subtle clinical ictal phenomena during the EEG patterns mentioned above, *OR*
  - Typical spatiotemporal evolution*

If EEG improvement occurs without clinical improvement or if fluctuation without definite evolution, this should be considered possible NCSE

* Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing

(Source: Beniczky et al. 2013.)

Differential diagnosis

Differential diagnosis	Features
Persistent non-convulsive seizures vs. prolonged postictal state, medication effects, or from underlying neurologic condition that caused the seizures	Persistent decreased consciousness after cessation of convulsive seizures
Seizures, tremor, clonus, or dyskinesia	Abnormal involuntary movements

Typical presentation

- CSE is manifested by repetitive generalized tonic-clonic seizures without return to baseline in between seizures. After convulsive seizures stop, the patient can still have electrographic status epilepticus with no apparent abnormal body movement. So if the patient does not show significant improvement in the level of consciousness within 10–20 minutes after the movement stops, the clinician should suspect ongoing NCSE and an EEG should be performed urgently.
- Focal NCSE can present as very subtle changes, such as mild confusion, mouth or hand automatism, speech arrest, eye deviation, nystagmus, or subtle twitching.

Clinical diagnosis

History

- History should include the onset of seizure or altered mental state, time course, past medical history including prior history of seizures or epilepsy, medications and recent medication changes, history of drug or alcohol abuse, etc.
- It is important to get collateral history from the family or a person who knows the patient well.
- Any function the brain is capable of generating can manifest as a symptom of NCSE, such as subtle behavioral or cognitive changes, autonomic disturbance, or motor/sensory disturbance.

Physical examination

- In addition to typical general and neurologic examination, observe subtle signs such as:
  - Behavioral/cognitive/sensory: agitation, amnesia, anorexia, aphasia, catatonia, coma, confusion, delusion, echolalia, laughter, lethargy, perseveration, personality changes, psychosis, singing.
  - Autonomic: abdominal sensation, apnea/hyperventilation, brady- and tachyarrhythmia, chest pain, flushing, miosis/mydriasis/hippus, nausea/vomiting.
  - Motor: automatisms, dystonic posturing, eye blinking, eye deviation, facial twitching, finger twitching, nystagmus, tremulousness.

Disease severity classification

- Refractory status epilepticus is defined as recurrent seizure activity despite two appropriately selected and dosed antiepileptic drugs, including benzodiazepine.
- Super-refractory status epilepticus refers to status epilepticus that continues or recurs 24 hours or more after the initiation of anesthetic drugs.

Laboratory diagnosis

List of diagnostic tests

- Serum glucose, antiepileptic drug levels, acid–base disturbances, arterial blood gas, basic metabolic panel, lactic acid, creatine kinase, troponin, transaminases, ammonia, calcium, magnesium, phosphorus, intoxications (alcohol level, urine toxicology), HCG (female).
- CSF: cell count, glucose, protein, Gram stain and culture (when an infectious or inflammatory etiology is suspected, the threshold for lumbar puncture should be low in patients with no history of epilepsy or seizures and no apparent CT head findings, and even in patients with epilepsy whose seizure frequency is usually low).
- Serum and/or CSF autoimmune/paraneoplastic panel (when clinically suspected).
- Brain and/or meningeal biopsy: in patients whose thorough evaluation is non-diagnostic and if any ill-defined lesion is present on MRI.

List of imaging techniques

- CT head: indicated in all patients unless the history offers an obvious explanation for the status epilepticus.
- Brain MRI: in patients whose etiology is not established after history, basic laboratory evaluation, lumbar puncture, and CT head.
- Chest/abdomen/pelvis CT: in patients who are suspected to have autoimmune/paraneoplastic encephalitis.
- Ovarian or testicular ultrasound: in patients who are suspected to have NMDA encephalitis.
- Angiogram: in patients who are suspected to have vasculitis.

Potential pitfalls/common errors made regarding diagnosis of disease

- Sometimes, patients who are having a cluster of non-epileptic seizures are misdiagnosed as having convulsive status epilepticus and it can lead to iatrogenic complications.
- Psychogenic status epilepticus should be suspected when:
  - Convulsions are prolonged without accompanying signs of sympathetic activation.
  - There is pelvic thrusting, eye closure, or asynchronous or side-to-side body or head movement.
  - There is minimal postictal confusion between or after convulsions.
  - There are bilateral convulsions with preserved consciousness.

Treatment

Diagnosis of status epilepticus, evaluation for the etiology, and management of status epilepticus should occur simultaneously. Patients who present with convulsive status epilepticus should receive treatment without delay. Patients who are suspected to have NCSE should have urgent continuous EEG monitoring.

Treatment rationale

- First line therapy: the first line treatment of choice in CSE is a benzodiazepine. If IV access is established, use IV lorazepam. If IV access is not established, use IM, nasal, or buccal midazolam or rectal diazepam.
- Second line therapy: even if the seizures stop after first line therapy, it is recommended to initiate second line therapy to prevent seizures from returning when the effect of the benzodiazepines wears off. The

choice of second line therapy is guided by the patient's etiology and comorbidities. Fosphenytoin is often recommended for this, but if the patient has idiopathic generalized epilepsy, valproic acid may be a better choice. Randomized controlled trials have shown that IV valproate is not inferior and may even be more effective than IV phenytoin.

- Failure of second line therapy = refractory status epilepticus. For generalized CSE or NCSE with severe impairment of consciousness, if seizures continue after one first line and one second line drug, it is recommended to start anesthetic drugs to prevent acute systemic complications, with initial bolus or repeated boluses followed by continuous infusion. If the patient is awake or has mild alteration of consciousness, it is recommended postponing the use of anesthetic drugs and try more than one second line drugs. The NCS guidelines recommend at least 24–48 hours of electrographic seizure control before slowly withdrawing the drug, which is usually done over 24 hours.
- Failure of anesthesic drugs = super-refractory status epilepticus. When seizures do not stop or recur after withdrawal of anesthesic medications, therapeutic options include a second trial of the same anesthetic drug, switching to another anesthetic drug, or a combination of anesthetic drugs. Other therapies including immune therapies, ketogenic diet, hypothermia, neurosurgery, and electroconvulsive therapy could be considered.

When to hospitalize

- Patients who present with status epilepticus should be hospitalized for proper evaluation and management.
- Patients who have refractory CSE or who are suspected of having NCSE should be managed in an ICU that can provide continuous EEG.

Managing the hospitalized patient

- The priority is always to ensure ABC (airway, breathing, circulation).
- Check finger-stick glucose, and, if low, give thiamine 100 mg IV once prior to dextrose.
- Initiate first line therapy and consult neurology.

Table of treatment: anticonvulsant drugs for status epilepticus

Treatment	Loading dose/ route	Maintenance dose	Mechanism of action	Adverse reactions
First line agents				
Lorazepam	0.1 mg/kg up to 4 mg IV	n/a, repeat loading dose once if necessary	GABA agonist	Respiratory depression, sedation, hypotension
Midazolam	0.2 mg/kg up to 10 mg IM	n/a, repeat loading dose once if necessary	GABA agonist	Same as above
Diazepam	0.2 mg/kg up to 20 mg rectally or 0.1 mg/kg up to 10 mg IV	n/a, repeat loading dose once if necessary	GABA agonist	Same as above

(Continued)

(*Continued*)

Treatment	Loading dose/ route	Maintenance dose	Mechanism of action	Adverse reactions
Second line agents				
Phenytoin	18–20 mg/kg IV up to 50 mg/min	5–7 mg/kg/day PO/IV divided every 8 hours	Sodium channel modulation	Cardiorespiratory depression, arrhythmia, hypotension, metabolic acidosis, infusion site injury
Fosphenytoin	18–20 phenytoin equivalents/kg IV up to 150 mg/ min	5–7 phenytoin equivalents/kg/ day IV, divided every 8 hours	Sodium channel modulation	Cardiorespiratory depression, arrhythmia, hypotension, non-allergic pruritis
Valproate sodium	25–40 mg/kg IV up to 3 mg/kg/ min	30–60 mg/kg/ day, divided every 6 hours	Multiple, including sodium channel modulation, GABA potentiation, glutamate/NMDA inhibition	Hyperammonemia, thrombocytopenia, pancreatitis, hepatic toxicity in children <2 years old
Levetiracetam	2000–4000 mg IV up to 500 mg/ min	2–12 g/day PO/ IV, divided up to every 6 hours	Synaptic vesicle protein 2 A	No major adverse reaction
Lacosamide	200–400 mg IV over 5 minutes	400–600 mg/ day IV, divided every 12 hours	Sodium channel modulation	May prolong PR interval
Phenobarbital	20 mg/kg IV up to 60 mg/min	1–4 mg/kg/day PO/IV, divided every 6–8 hours	GABA potentiation	Sedation, respiratory depression
Third line agents				
Midazolam	0.2 mg/kg IV	0.1–2 mg/kg/h	GABA potentiation	Sedation, respiratory depression, hypotension
Propofol	1–2 mg/kg IV	2–12 mg/kg/h	GABA agonist, glutamate/NMDA inhibition, calcium channel modulation	Sedation, respiratory depression, hypotension, propofol infusion syndrome (acidosis, multiple organ failure, rhabdomyolysis)
Ketamine	1.5–4.5 mg/kg IV	2.75–5 mg/kg/h	Glutamate/NMDA inhibition	Hypertension, possible rise in intracranial pressure
Pentobarbital	5–15 mg/kg IV administered over 1 hour	0.5–5 mg/kg/h	GABA potentiation	Sedation, respiratory depression, hypotension, ileus, gastric stasis, metabolic acidosis, thrombocytopenia, immunosuppression

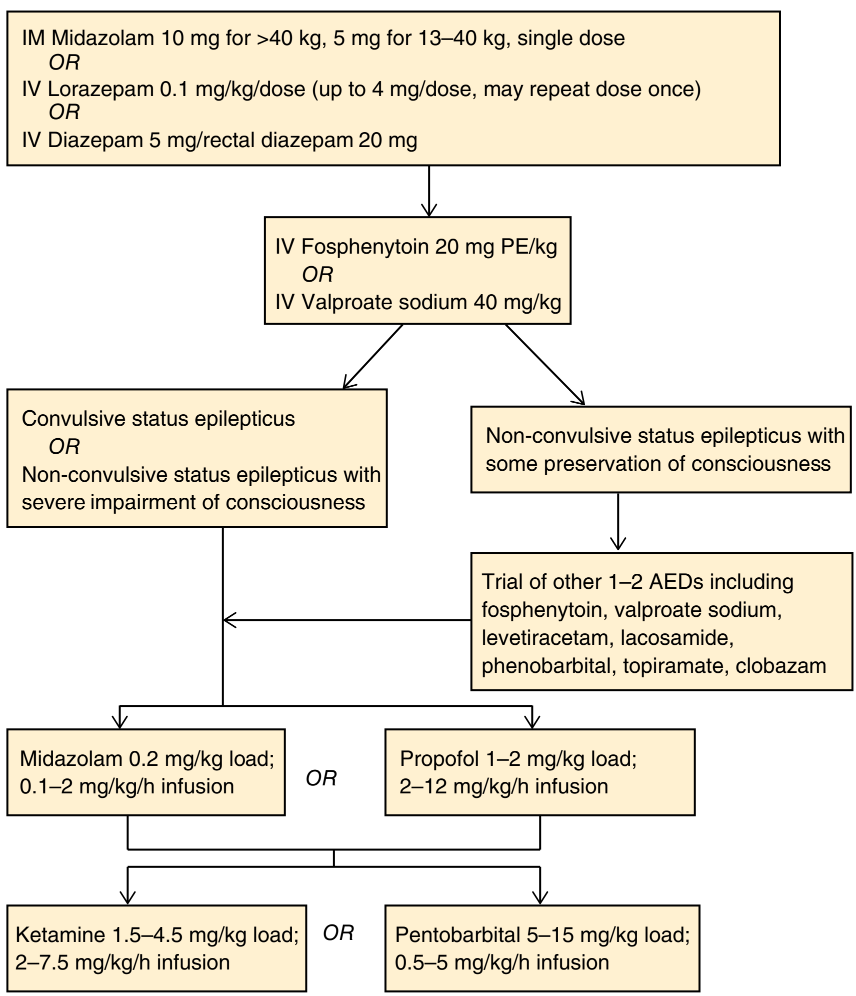
Prevention/management of complications

A meta-analysis reviewing of refractory status epilepticus treatment endpoints showed:

- A significant higher rate of breakthrough seizures when cessation of electrographic seizures was used as a treatment goal.
- A higher rate of treatment-related complications when background suppression was the target.
- Continuous EEG can therefore be used to optimize treatments by maximizing seizure control and minimizing adverse effects.

Treatment algorithm (Algorithm 29.1)

Algorithm 29.1 Treatment of status epilepticus



CLINICAL PEARLS

- CSE is an emergency and must be treated aggressively. The longer the seizure lasts, the more refractory the patient becomes to treatment.
- Continuous EEG is required to diagnose NCS or NCSE.
- Management of NCSE can be different to that of CSE. Careful considerations should be made about the ultimate prognosis of the individual patients.

Special populations

Children

- A different treatment sequence is used for newborns. Phenobarbital is used first line with a loading dose of 20 mg/kg with two additional 10 mg/kg doses if seizures continue (goal is a serum level of at least 40 μg/L). If seizures continue, either midazolam or fosphenytoin can be used next.
  - Midazolam: IV loading dose 0.15 mg/kg, with additional dose of 0.10–0.15 mg/kg given 15–30 minutes later if seizures continue.
  - Fosphenyotin: IV loading dose 20 mg/kg, given at a rate of 0.5–1 mg/kg/min.
- In children in refractory status epilepticus, midazolam and pentobartibal are preferred agents than propofol, as the latter has a higher incidence of adverse events such as propofol infusion syndrome.

Others

- In patients with kidney or liver dysfunction, a loading dose of AEDs is the same but the maintenance dose needs to be adjusted according to levels.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- The prognosis for adults who present with status epilepticus depends largely upon the underlying etiology.
- Negative prognostic factors include older age, longer duration, subtle status epilepticus after generalized CSE, female sex, and the presence of comorbidities.
- Between 20% and 50% of survivors will have significant functional disability. Worse outcome is more common in patients with acute brain injury and after refractory status epilepticus, however meaningful recovery is still possible.

Reading list

Beniczky S, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia 2013;54:28–9
Hirsch LJ, Brenner RP. Atlas of EEG in Critical Care, 2nd edition, Oxford: Wiley Blackwell, 2010.
Kaplan PW, Drisland FW. Nonconvulsive Status Epilepticus. New York: Demos Medical, 2009.
LaRoche SM. Handbook of ICU EEG Monitoring. New York: Demos Medical, 2013.
Lee K. The Neuro ICU Book. New York: McGraw-Hill, 2012.
LeRoux, PD, Levine, JM, Kofke, AW. Monitoring in Neurocritical Care. Philadelphia: Elsevier.

Suggested websites

www.acnsorg
www.neurocriticalcare.org

Guidelines

National society guidelines

Title	Source and comment	Date and reference
Guidelines for the Evaluation and Management of Status Epilepticus	Neurocritical Care Society	2012 Brophy GM, et al. Neurocrit Care 2012;17:3–23
Evidence-based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults	American Epilepsy Society	2016 Glauser T, et al. Epilepsy Curr 2016;16(1):48–61

Evidence

Type of evidence	Title and comment	Date and reference
RCT	*A comparison of four treatments for generalized convulsive status epilepticus.* Compared the efficacy of lorazepam, diazepam plus phenytoin, phenobarbital, or phenytoin, and found that IV lorazepam was superior to IV phenytoin in stopping seizures lasting at least 10 minutes	1998 Treiman DM, et al. N Engl J Med 1998;339:792–8
RCT	*A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus.* Both lorazepam and diazepam were superior to placebo	2001 Alldredge BK, et al. N Engl J Med 2001;345:631–7
RCT	*Intramuscular versus intravenous therapy for prehospital status epilepticus*: IM midazolam has superior effectiveness compared with IV lorazepam in adults with convulsive status epilepticus without established IV access	2012 Silbergleit R, et al. N Engl J Med 2012;366:591–600

Additional material for this chapter can be found online at: www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions and case study.

with website

CHAPTER 30

Intracranial Pressure and Neuromonitoring

Pavis Laengvejkal[1] and Stephan A. Mayer[2]
[1]Bumrungrad International Hospital, Bangkok, Thailand
[2]New York Medical College, Valhalla, NY, USA

OVERALL BOTTOM LINE

- Intracranial pressure (ICP) monitoring is essential for reducing secondary injury for comatose patients with severe brain injury.
- Multimodality neuromonitoring allows for brain tissue oxygen, cerebral blood flow, and brain chemistry measurements (microdialysis).
- Continuous EEG monitoring is essential for detecting non-convulsive seizure activity, which occurs in 10–30% of comatose patients.

Intracranial pressure monitoring

Overview

- ICP represents the pressure within the dura.
- The normal value is 3–15 mmHg (or 5–20 cmH_2O).
- Increased ICP leads to cerebral ischemia and herniation and requires immediate treatment.

Monro–Kellie doctrine

- The Monro–Kellie doctrine states that the cranial vault is a fixed space containing three volumes: blood, cerebrospinal fluid (CSF), and brain.
- Any space-occupying lesion or increased volume of intracranial constituents may lead to increased ICP.

Intracranial compliance

- Intracranial compliance is defined as the change in volume over the change in pressure (dV/dP).
- Compliance decreases as intracranial volume increases (Figure 30.1).
- In the initial phases of an ICP-elevating process, as volume is added to the skull (point A), CSF is displaced into the spinal thecal sac and blood is decompressed from the distensible cerebral veins.
- If compensatory redistribution mechanisms are exhausted ICP can increase profoundly with small increments of additional volume (point B).
- The amplitude of the ICP pulse wave may provide a clue that compliance is reduced; as compliance falls, the ICP pulse amplitude increases (point B, inset).

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Cerebral perfusion pressure

- Cerebral perfusion pressure (CPP) is calculated as mean arterial pressure (MAP) minus ICP.
- A consequence of elevated ICP is lowering of cerebral blood flow (CBF) and secondary hypoxic–ischemic injury.
- CPP determines CBF and should remain above 60 mmHg.
- Autoregulation of the cerebral vasculature maintains CBF at a constant level of between 50 and 100 mmHg. Brain injury can impair autoregulation and cause CBF to approximate a more straight line relationship with CPP (Figure 30.2).

Pathologic pressure waves

- In patients with raised ICP, pathologic ICP waveforms may occur (Figure 30.3).
- Lundberg A waves (or plateau waves) represent prolonged periods of profoundly high ICP. They are ominous, and abruptly occur when either CPP or intracranial compliance is low. Their duration is from minutes to hours, and levels as high as 50–100 mmHg may be reached.
- Lundberg B waves are of shorter duration and have lower amplitude elevations that indicate that intracranial compliance reserves are compromised.

Conditions associated with increased ICP

I. Intracranial mass lesions
- Subdural hematoma
- Epidural hematoma
- Brain tumor
- Cerebral abscess
- Intracerebral hemorrhage

II. Increased brain volume (cytotoxic edema)
- Cerebral infarction
- Global hypoxia-ischemia
- Reye's syndrome
- Acute hyponatremia

III. Increased brain and blood volume (vasogenic edema)
- Hepatic encephalopathy
- Traumatic brain injury
- Meningitis
- Encephalitis
- Hypertensive encephalopathy
- Eclampsia
- Subarachnoid hemorrhage
- Dural sinus thrombosis
- Eclampsia

IV. Increased CSF volume
- Communicating hydrocephalus
- Non-communicating hydrocephalus
- Choroid plexus papilloma

Clinical features of elevated ICP

- Clinical manifestations of increased ICP are varied and unreliable.
- Features include depressed level of consciousness, nausea and vomiting, headache, blurring of vision, and diplopia (from sixth nerve palsies).
- Cushing's triad may be observed: increased arterial blood pressure associated with bradycardia and irregular respirations.
- Increased ICP can lead to herniation syndromes, which result from brain tissue shifting related to compartmentalized pressure gradients.

Herniation syndromes

Type	Clinical hallmark	Causes
Uncal (lateral transtentorial)	Ipsilateral CN3 palsy Contralateral or bilateral motor posturing	Temporal lobe mass lesion
Central transtentorial	Progression from bilateral decorticate to decerebrate posturing Rostral–caudal loss of brainstem reflexes	Diffuse cerebral edema, hydrocephalus
Subfalcine	Asymmetric (contralateral > ipsilateral) motor posturing Preserved oculocephalic reflex	Convexity (frontal or parietal) mass lesion
Cerebellar (upward or downward)	Sudden progression to coma with bilateral motor posturing Cerebellar signs	Cerebellar mass lesion

Indications for ICP monitoring

Patients should generally meet three criteria prior to placement of an ICP monitor:

- Brain imaging reveals a space-occupying lesion or cisternal effacement suggesting that the patient is at risk for high ICP.
  - The patient is comatose (GCS score of ≤8).
  - The prognosis is such that aggressive ICU treatment is indicated.

ICP monitoring devices

- Several types of ICP monitors exist.
- The external ventricular drainage (EVD) catheter is the gold standard; it consists of a water-filled catheter which is placed through a burr hole into the ventricle and connected to a pressure transducer set at head level.
- EVD allows for both ICP monitoring and the ability to perform therapeutic CSF drainage.
- A major drawback of EVD is the risk of infectious ventriculitis, which occurs in approximately 10–15% of patients and steadily increases until the 10th day of use.
- The best alternatives to EVD include fiberoptic transducers (Integra®) or pressure microsensors (Codman®) placed through a burr hole either into the parenchyma or ventricle. These devices carry a minimal risk of infection and are highly reliable.

Treatment of ICP

There are two scenarios for ICP management:

- Hyperacute situation during which brain herniation is taking place. Treatment is an all-out approach to immediately protect the brainstem pending definitive surgical intervention or placement of an ICP monitor:
  - Elevate head of bed 30–45°.
  - Normal saline (0.9%) at 80–100 mL/h (avoid hypotonic fluids).
  - Intubate and hyperventilate (target PCO_2 = 28–32 mmHg).
  - Mannitol 20% 1–1.5 g/kg via rapid IV infusion.
  - Foley catheter.
  - CT scan and immediate neurosurgical consultation.

- Monitored patients in the ICU setting. This algorithm should be initiated any time ICP remains greater than 20 mmHg for more than 10 minutes:
  - Consider repeat CT scanning and surgical removal of an intracranial mass lesion, or ventricular drainage.
  - Intravenous sedation with fentanyl and propofol to attain a motionless, quiet state.
  - Reduction of blood pressure if CPP remains >110 mmHg, or vasopressor infusion if CPP <70 mmHg.
  - Mannitol 0.25–1 g/kg IV (repeat every 1–6 hours as needed).
  - Hyperventilation to PCO_2 levels of 28–32 mmHg.
  - Paralysis with neuromuscular blockade.
  - High dose pentobarbital therapy (load 5–20 mg/kg and infuse 1–4 mg/kg/h).
  - Hypothermia with external cooling to 32–34°C.

Multimodality neuromonitoring

Brain oxygenation monitoring

- The human brain consumes 20% of total body oxygen.
- Approximately 90% of the energy is used by neurons, mainly for synaptic activity and to preserve ionic gradients. The energy substrate is high energy phosphate (ATP), produced from glucose through aerobic metabolism.
- In the absence of continuous oxygen delivery, ATP production ceases within seconds. Osmotic gradients are lost, edema sets in, intracellular calcium rises, and early apoptotic mechanisms are triggered.
- With new technology early detection and reversal of brain hypoxia is feasible. Two invasive bedside techniques allow for brain oxygenation monitoring: brain tissue oxygen partial pressure ($PbtO_2$) and jugular venous oxygen saturation ($SjvO_2$) monitoring.
- Both $SjvO_2$ and $PbtO_2$ are dependent on CBF, arterial O_2 content, and cerebral metabolic rate of O_2 consumption ($CMRO_2$). $AVDO_2$, the arteriovenous difference in O_2 content, can be simplified as $SaO_2 - SjvO_2$, since other parameters, like hemoglobin, remain constant during cerebral transit.

$$CMRO_2 = CBF \times AVDO_2\text{, where } AVDO_2 \approx SaO_2 - SjvO_2$$

Jugular venous oxygen saturation monitoring

- This technique employs continuous oximetry in the jugular bulb to analyze oxygen content of cerebral venous drainage.
- Normal $SjvO_2$ values range between 55% and 75%.
- Low values suggest insufficient O_2 delivery to the brain to meet metabolic needs, which may reflect high $CMRO_2$, low CBF, or both.
- $SjvO_2$ values above 75% suggest hyperemia from loss of autoregulation, resulting in excessive cerebral vasodilation, which can occur after traumatic brain injury (TBI) or in disuse inflammatory states, or low oxygen consumption, which can occur with hypothermia, barbiturate anesthesia, or extensive cerebral infarction.

Brain tissue oxygen pressure monitoring

- The most commonly used technologies for $PbtO_2$ measurement today are based on use of a Clark electrode (Licox®) and oxygen quenching methods using a microchip at the catheter tip (Raumedic).
- The tip of the probe should be located in the white matter, where normal $PbtO_2$ levels range from 25 to 50 mmHg.
- A post-insertion CT scan is mandatory to confirm positioning and interpret readings, since placement in hemorrhagic or infarcted tissue results in uninterpretable readings near zero.
- A low $PbtO_2$ can help detect a new critical event, like vasospasm after subarachnoid hemorrhage or seizure. A reassuring value, on the contrary, may be an argument for permissive ICP. $PbtO_2$ change is a way to evaluate the patient's response to delayed cerebral ischemia (DCI) treatment with hemodynamic augmentation therapy. It can also be used to carefully titrate hyperventilation therapy, or to detect a detrimental ventilation strategy.

Cerebral blood flow monitoring

- CBF monitoring is meant to detect hypoperfusion before it leads to irreversible ischemia, while it is still amenable to treatment.
- Two available continuous bedside modalities are available: thermal diffusion flowmetry (TDF) and laser Doppler flowmetry (LDF).

Thermal diffusion flowmetry

- TDF is an invasive technique that allows quantitative continuous measurement of regional CBF measured in mL/100g/min.
- The probe is inserted 25 mm into the brain and comprises a thermistor at the tip and a temperature sensor a few millimeters proximal.
- Since the probe is located in the subcortical white matter, 15 mL/100g/min is a reasonable threshold for defining critical hypoperfusion.
- Low CBF values alone, however, do not necessarily imply active ischemia, since low CBF can also be coupled to a low rate of cerebral metabolism. Concurrent $PbtO_2$ or $SjvO_2$ monitoring is helpful differentiating low CBF states.

Laser doppler flowmetry

- LDF is an invasive technique that provides continuous qualitative assessment of local microvascular perfusion.
- The fiberoptic laser probe emits laser light, illuminating approximately 1 mm^3 of brain tissue, and the photoreceptor detects a portion of the light that is scattered back.
- The frequency shift of the light, based on the Doppler effect paradigm, allows for evaluation of red blood cell velocities.
- Although correlation with gold standard measurements of CBF is high, LDF does not provide absolute CBF values and can only be used as a trend monitor. It is prone to many artifacts and has limited use in neurocritical care units.

Cerebral microdialysis

- Brain function is dependent on ATP production. One molecule of glucose is metabolized to pyruvate and, in the presence of oxygen, will enter the Krebs cycle.
- In the absence of oxygen, pyruvate will be metabolized into lactate, a much less efficient energy-producing pathway. Lactate can be used as a source of energy production by neurons when glucose is unavailable.
- In the presence of catecholamines or fever, the whole glycolysis process is accelerated, resulting in elevation of lactate and pyruvate levels.
- If hypoxemia is present, only lactate will increase, as pyruvate is anaerobically consumed, with lactate as an end product. This is the logic behind the use of the lactate : pyruvate ratio (LPR) to detect anaerobic metabolism, an important physiologic marker of ischemia.
- Glutamate is the main excitatory amino acid in the neuron. Metabolic failure will lead to elevated glutamate levels.
- Glycerol is also a marker of advanced cellular damage. When cellular metabolism fails, one of the final common pathways is loss of cellular integrity and membrane degradation. Release of phospholipids ensues, which are converted to free fatty acids and glycerol.
- Microdialysis allows for bedside monitoring of brain tissue biochemistry. The probe is a 0.6 mm double lumen catheter with a semipermeable membrane that allows free diffusion of water and solutes down a concentration gradient. Isotonic fluid is perfused at a constant rate of 0.3 μL/min and the perfusate is collected and analyzed hourly. The probe is usually 2 cm deep, close to the white matter.

- One of the most clinically useful indices is the LPR. Values over 20–25 correlate with worse outcome in TBI and subarachnoid hemorrhage (SAH) patients, and a ratio over 40 is used to define 'metabolic distress.'
- Low brain glucose levels (normally 1–2 mmol/L) are also related to outcome in SAH and TBI patients, especially when less than 0.50 mmol/L. An LPR ratio greater than 40 combined with a brain interstitial glucose level <0.5 mmol/L is termed 'metabolic crisis,' and is associated with poor outcome and a high risk of death among comatose patients.
- A useful aspect of microdialysis monitoring is that derangements can precede impending deterioration, including elevated ICP in TBI patients or delayed neurologic injury in SAH patients. Severe derangements can be used to trigger emergent decompressive neurosurgical intervention, induction of hypothermia, or angiography to reverse ongoing ischemia.

Intracortical (or depth) EEG monitoring

- Intracortical (or depth) EEG monitoring is an invasive form of focal electrical brain monitoring that can been used in addition to multimodality monitoring of CBF and $PbtO_2$ to determine whether these ictal–interictal patterns are truly ictal or not.
- Intracortical EEG has two to three times the sensitivity of surface EEG for detecting electrographic seizures in comatose patients.

Continuous electroencephalogram monitoring

- Continuous (cEEG) monitoring is an essential tool in neurocritical care.
- Specific uses include detection of seizures, titration of therapy for status epilepticus, monitoring for DCI in SAH patients, and coma prognostication.

Seizure detection

- Between 10% and 50% of comatose patients have non-convulsive seizures or non-convulsive status epilepticus (NCSE) when monitored with cEEG depending on the primary diagnosis, and the vast majority are clinically undetectable. Non-convulsive seizures can directly produce depressed level of consciousness and are associated with poor outcome after all forms of acute severe brain injury.
- Duration of monitoring is an important factor in the ability to detect seizures: a 30 minute spot EEG has approximately one-third the sensitivity of a 24 hour cEEG study. A minimum of 48 hours of cEEG monitoring is required to attain >90% sensitivity for detecting non-convulsive seizures or NCSE.

Titration of therapy for status epilepticus

- cEEG is mandatory for guiding therapy for refractory status epilepticus.
- Delays in efficient treatment of SE leads to less therapeutic success and higher mortality.
- Almost 50% of patients who present with convulsive status epilepticus who fail to recover consciousness after initial therapy continue to have evidence of non-convulsive seizures or NCSE.
- The EEG target of continuous infusion treatments for NCSE (i.e. midazolam, propofol, ketamine, or pentobarbital) can range from simple elimination of ictal discharges to induction of burst suppression, depending on the clinical scenario.

Monitoring for DCI after SAH

- cEEG is very sensitive to brain physiology, and changes in the EEG pattern are a promising way to detect DCI after SAH.
- Reduction in alpha-variability and the alpha/delta ratio have been found to signal the imminent onset of DCI. Most interestingly, those changes can precede the onset of clinical symptoms by 1–2 days.

Coma prognosis

- EEG is the most widely used prognostic tool to support a clinical examination and is accessible in most hospitals.
- Highly malignant EEG patterns are found to be associated with poor outcome (Figure 30.4):
  - Suppressed background without discharges.
  - Suppressed background with continuous periodic discharges.
  - Burst suppression background with or without discharges.

Limitations of cEEG

- The main limitations of cEEG monitoring are technical and logistic.
- The recordings are subject to multiple artifacts, from eye movement to electrostatic artifacts.
- The continuous recordings constitute an incredible amount of data to be interpreted, and conclusions can vary from one reader to another.
- Automated systems are being developed, but cEEG remains for now a cost- and labor-intensive modality requiring expert technical and medical staff.

Reading list

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Images

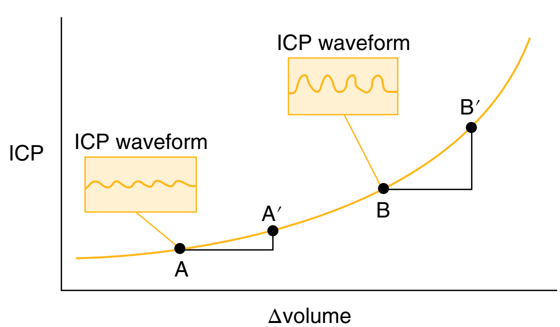

Figure 30.1 Intracranial pressure–volume curve. At point A, on a flatter portion of the curve, the amplitude of the arterial reflection in the ICP waveform is small (inset), and the addition of the same amount of volume leads to a smaller increase in pressure (A′). At point B, on a steep portion of the curve, the intracranial compartment is relatively non-compliant, the amplitude of the arterial reflection in the ICP waveform is large (inset), and the addition of volume leads to a large increase in pressure. (Source: Mayer 1997.)

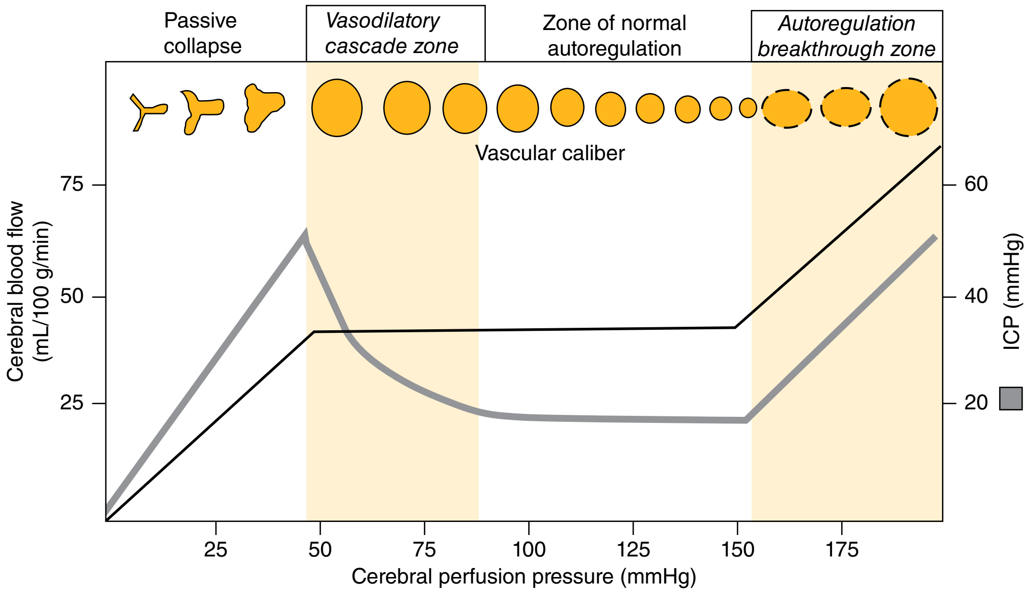

Figure 30.2 Cerebral autoregulation curve (black line) and relationship between CPP and ICP in states of abnormal intracranial compliance (gray line). Under normal circumstances CBF is held constant across a wide range of CPP (50–150 mmHg), and changes in vessel caliber have no effect on ICP. In disease states with reduced intracranial compliance, however, ICP can become elevated when CPP is low due to autoregulatory vasodilation and increased cerebral blood volume (CBV) (vasodilatory cascade physiology), or when CPP is too high due to passive increases in CBV due to increased hydrostatic pressure and hyperemia (autoregulation breakthrough physiology).

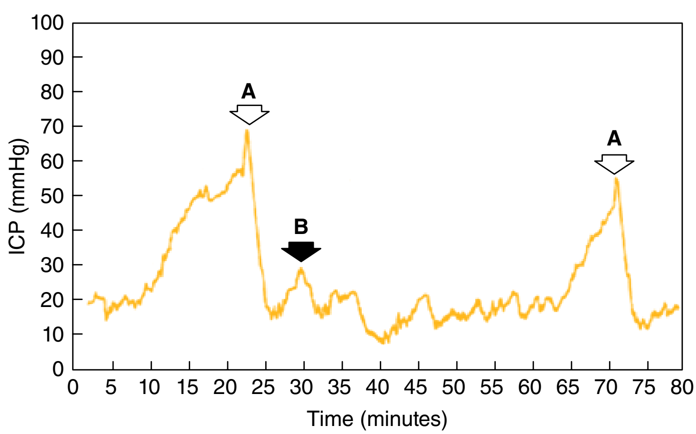

Figure 30.3 Pathologic ICP waves: A, Lundberg A (plateau) waves, and B, Lundberg B waves.

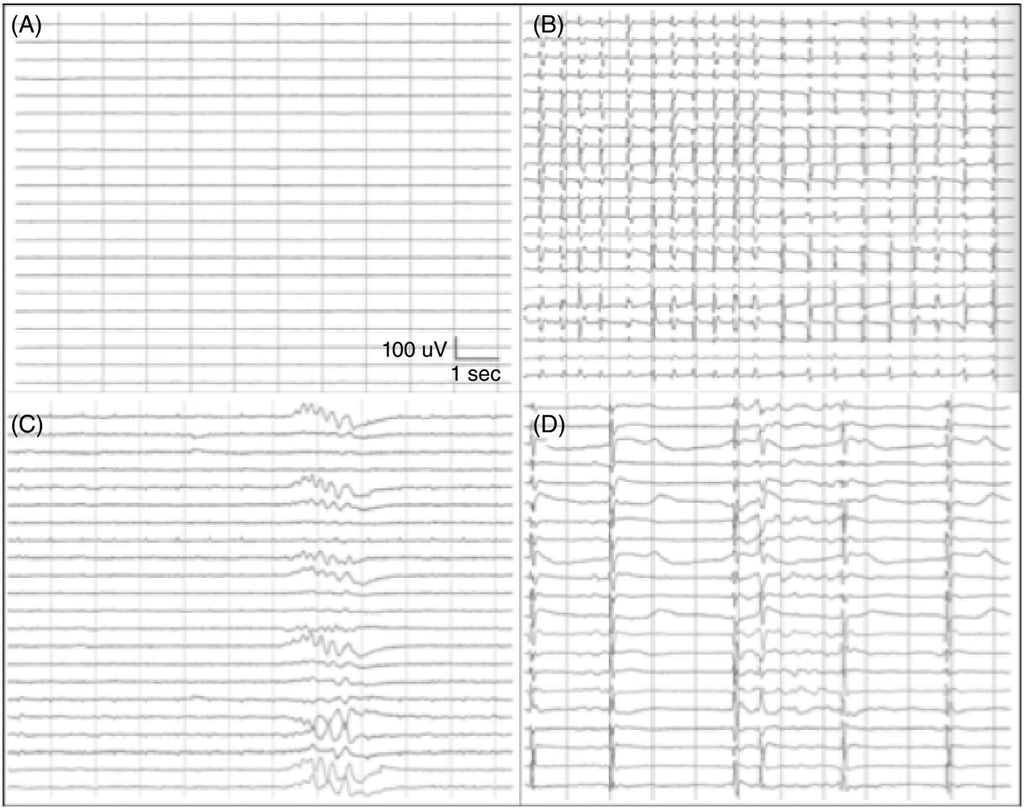

Figure 30.4 (A) Suppressed background. (B) Suppressed background with continuous periodic discharges. (C) Burst suppression without discharge. (D) Burst suppression with superimposed discharges.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 31

Coma and Brain Death

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OVERALL BOTTOM LINE

- Disorders of consciousness are disorders that affect a person's ability to be alert (wakefulness), and ability to be aware of oneself or one's environment.
- Coma is a severe state of cerebral dysfunction resulting from either structural, chemical, electric, or toxic disorders of the brain. Coma is potentially reversible and life threatening and should be treated as a medical emergency.
- Brain death is the irreversible cessation of all brain function.
- The determination of brain death is made in accordance with acceptable medical standards and local laws.

Background

- Disorders of consciousness are conditions that affect a person's ability to be alert and aware of one's environment. Operationally, levels of consciousness can be thought of as being on a spectrum. A person who is fully conscious is alert and can fully perceive themselves and their environment.
- *'Locked-in' syndrome*: a person who is suffering from a 'locked-in' syndrome may also be fully conscious, but has a limited ability to purposefully interact with their environment. Classically, they may have preserved volitional vertical eye movements and eye opening.
- *Minimally conscious state*: often develops weeks to months after a severe cerebral injury wherein the person was comatose. Individuals in this state may show some subtle signs of interacting with their environment such as visually tracking, orienting to pain, or intermittently following commands. These individuals are not able to communicate their thoughts or feelings.
- *Persistent vegetative state*: individuals who are in a 'vegetative' state or 'coma vigil' have intact circadian rhythms, eye opening, and preserved automatic functions.
- *Coma*: patients with severe cerebral dysfunction who are unresponsive are said to be in a coma. This may result from several life-threatening conditions including structural injuries, vascular pathology, toxicity from drugs, other metabolic disarrangement, or epileptic abnormality. Coma may be potentially reversible.
- *Brain death*: a person who has been determined to be 'brain dead' has suffered irreversible cessation of all brain function. Brain death is a concept not known prior to the advent of ventilators. The determination of brain death is based on accepted medical practices and local law.

Disease classification

The Glasgow Coma Scale (GCS) is often used to describe a person's level of consciousness after injury or medical event. The score is divided in to three sections (eye, verbal, and motor). Each section is given a

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numerical value based on the patient's best response. The sum of all three values provides the score. The scale is graded from 3 to 15 and individuals who score 8 or less are considered to be in a coma.

Eye response	Verbal response	Motor response
4. Spontaneous eye opening	5. Oriented	6. Following commands
3. Eye opening on verbal command	4. Confused	5. Localizes to pain
2. Eye opening to pain	3. Inappropriate words	4. Withdrawal from pain
1. No eye opening	2. Incomprehensible sounds	3. Flexion in response to pain
	1. No verbal response	2. Extension in response to pain
	T. Endotracheal tube placement	1. No motor response

Etiology of coma

- *Trauma*: contusions, diffuse axonal injury, Duret hemorrhage.
- *Toxins*: lead, carbon monoxide, cyanide.
- *Drugs*: sedative medications including benzodiazepines, barbiturates, opiates.
- *Metabolic derangements*: hypoxia, hypotension, hypothermia, hyperthermia, hyponatremia, hypernatremia, hypothyroidism, hepatic encephalopathy, uremia, dialysis disequilibrium syndrome, porphyria, diabetic ketoacidosis, hyperosmolar non-ketotic coma.
- *Infections*: bacterial meningitis, brain abscesses, epidural abscesses, viral encephalitis.
- *Vascular*:
  - Intracranial hemorrhages: parenchymal hemorrhage, subarachnoid hemorrhage, epidural hemorrhage.
  - Ischemic infarctions: large hemispheric, brainstem, pons.
- *Seizures*: status epilepticus, epileptic encephalopathy.
- *Cerebral herniation*: subfalcine herniation, central herniation, uncal herniation, tonsillar herniation, upward herniation.
- *Inflammatory*: encephalitis, vasculitis.

Pathology/pathogenesis

- Coma may result from diffuse bilateral hemispheric dysfunction, significant injury to one hemisphere, or dysfunction in the ascending reticular activating system (ARAS).
- The ARAS is a network of neurons located in the midbrain and pons. These neurons have projections to the thalamus and hypothalamus, with subsequent connections to the cerebral cortex.
- Decorticate posturing: flexion in the upper extremities with extension of the lower extremities. Evidence of injury at the level of the cerebral cortex.
- Decerebrate posturing: extension of the upper extremities with extension of the lower extremities. Evidence of injury below the red nucleus.

Diagnosis

- Brain death is the determination of death by neurological criteria.
- Components of the brain death determination process include a clinical exam documenting the complete absence of all brain stem reflexes and an apea test documenting absent respirations in the setting of hypercarbia (pCO_2 >60 mm Hg).
- If providers are unable to complete part of the process or there is a confounding factor (e.g. drugs, CO_2 retention at baseline), the determination of brain death may be aided by a confirmatory test.

Differential diagnosis of coma or brain death

Differential diagnosis	Features
'Locked in' syndrome	Classically, patient with 'locked in' syndrome may have preserved vertical gaze and possibly eye opening
Drugs/intoxication	A careful history is needed and possible drug/alcohol laboratory screen is needed to exclude intoxication from the diagnosis of brain death
Guillain–Barré syndrome (GBS)	A careful history and physical exam is needed to differentiate GBS from brain death. Classically, GBS will have ascending paralysis with absent deep tendon reflexes. Deep tendon reflexes may be present in patients who are brain dead
Hypothermia	Core temperature should always be measured before beginning the determination of brain death
Neuromuscular paralysis/ neuromuscular-blocking agents	A train-of-four should be checked if there is concern for a neuromuscular blocking agent

Clinical diagnosis of brain death

Physical examination

- Prerequisites:
  - Identify proximate cause either through clinical history or CNS imaging of an acute injury compatible with brain death.
  - Assess the extent and potential reversibility of any damage.
  - Exclude factors including medical conditions that may confound clinical assessment, such as significant hypothermia (<36°C) or hypotension (SBP ≤100 mmHg, MAP ≤65 mmHg).
- Coma or unresponsiveness:
  - No cerebral response to pain in all extremities (nail bed pressure, supraorbital pressure).
- Pupils:
  - No response to bright light.
- Ocular movement:
  - No occulocephalic reflex: eyes appear to be painted on with head movement.
  - No oculovestibular reflex: no deviation of the eyes to irrigation in each ear of 60 mL of cold water.
- Facial sensation and motor response:
  - No corneal reflex.
  - No jaw reflex.
  - No grimacing to deep pressure on nail bed, supraorbital ridge, or temporomandibular joint.
- Pharyngeal and tracheal reflexes:
  - No response after stimulation of posterior pharynx.
  - No cough response to endotracheal suctioning.

Apnea test

- Prerequisites:
  - Core temperature >36.5°C.
  - Systolic blood pressure ≥100 mmHg.
  - Normal PCO_2 ($PaCO_2$ 40 mmHg).
  - Normal PO_2 (preoxygenate to a PO_2 >200 mmHg).
- Procedure:
  - Make sure patient is connected to a pulse oximeter. Disconnect from the ventilator. Deliver 100% oxygen into the trachea. This may be done via a cut nasal cannula tubing. Monitor for respiratory movements.

- Obtain arterial blood gas at around 7–8 minutes and reconnect to the ventilator.
- If respiratory movements are noted at any time, the test is not consistent with brain death.
- If SBP is <90 mmHg or patient develops arrhythmia or significant desaturations, obtain arterial blood sample and abort the test.
- Test is consistent with brain death if PCO_2 rises to >60 mmHg or rises 20 mmHg from baseline and no respiratory movements are observed.

Useful clinical decision rules when diagnosing brain death

- CNS depressants: if no ability to measure levels and assuming normal clearance, wait 5× half-life.
- For alcohol intoxication, wait until level is <0.80%.
- Train-of-four should be performed in patients with history of neuromuscular blockade.
  Neurologic exam is more reliable with SBP ≥100 mmHg or MAP ≥65 mmHg.
- One consistent neurologic and brainstem exam along with a consistent apnea test should be sufficient to pronounce brain death (must follow local laws).
- In cases where parts of the brain death determination process are unable to be performed, an ancillary test may be obtained in order to establish the diagnosis.

Laboratory diagnosis of brain death

List of diagnostic tests

- EEG: used in the first brain death declarations. EEGs are affected by medication and metabolic derangements that may be reversible. No electrical activity during at least 30 minutes of recording is consistent with the diagnosis of brain death.
- CTA: no intracerebral filling past the level of the circle of Willis while the external carotid circulation is patent and fills is consistent with the diagnosis of brain death.
- MRA: no intracerebral filling past the level of the circle of Willis while the external carotid circulation is patent and filling is consistent with the diagnosis of brain death.
- Catheter-based cerebral angiography: this is the traditional gold standard test. No intracerebral filling past the level of the circle of Willis while the external carotid circulation is patent and fills is consistent with the diagnosis of brain death. Absence of intracranial filling requires an ICP higher than the MAP.
- Nuclear medicine cerebral blood flow test: demonstration of no perfusion to the brain ('light bulb' sign) is consistent with the diagnosis of brain death.
- Transcranial Doppler: safe, non-invasive, and portable but requires a skilled operator. Systolic peaks with no diastolic flow leading to an oscillating or reverberating flow pattern is necessary for an exam to be consistent with the diagnosis of brain death.

Potential pitfalls/common errors made regarding diagnosis of brain death

- Certain lower motor neuron motor movements are still consistent with the diagnosis of brain death, including the following:
  - Facial myokymia.
  - Transient bilateral finger tremor.
  - Repetitive leg movements.
  - Ocular micro-tremor.
  - Cyclical constriction and dilation in light-fixed pupils.
  - Retained planter reflexes.
  - Undulating toe flexion.

CLINICAL PEARLS

- Identification of a proximate cause is required before undergoing brain death determination.
- Patients need to be at an adequate temperature and with an adequate blood pressure prior to brain death determination.
- Angiography shows opacification of the external carotid branches without opacification to the internal carotid distribution past the level of the circle of Willis.

Management of potential organ donors

- Brain death eventually leads to severe homeostatic derangements and cardiac arrest, despite mechanical ventilation and aggressive life support measures. This creates a challenge in managing the potential organ donor, in whom the goal is to maintain and optimize organ viability for transplantation.
- Most patients become hypotensive due to sudden loss of resting sympathetic tone and require IV pressors at the time brain death occurs. Soon thereafter, they develop diabetes insipidus (because antidiuretic hormone secretion ceases).
- Vasopressors such as norepinephrine or arginine vasopressin, both of which cause peripheral vasoconstriction in this setting, are considered the first line interventions for hypotension.
- In some cases, continued hypotension will respond to thyroid and glucocorticoid hormone replacement, indicating a relative deficiency of these hormones.

Procedure

- Insert a central venous catheter or two large bore peripheral IV lines.
- Insert an arterial line for continuous BP monitoring.
  - Maintain mean BP at or higher than 65 mmHg with stepwise intervention:
    - 1000 mL 0.9% saline fluid bolus (two times at 10 minute intervals).
    - Arginine vasopressin 4–6 U/h.
    - Norepinephrine 0.05–0.1 µg/kg/min IV infusion; titrate to effect, maximum 1–2 µg/kg/min.
    - If hypotension is refractory to norepinephrine and/or IV vasopressin, perform a thyroxine replacement protocol. Administer as IV boluses:
      - Dextrose 50% (1 amp).
      - Methylprednisolone 1 g.
      - Regular insulin 10 units.
      - Levothyroxine 20 µg.
    - If the BP responds to the above boluses, start levothroxine 5 µg/h as a continuous infusion (200 µg/500 mL NS at 12.5 mL/h) and titrate to maintain the SBP >100 mmHg. Note that thyroxine can precipitate cardiac arrhythmias, particularly in younger, hypokalemic patients.
- Start baseline IV flow: 0.9% saline at 100–200 mL/h.
  - Check serum sodium levels every 6 hours:
    - If sodium level is 150–159 mEq/L, change baseline IV to 0.45% saline.
    - If sodium level is ≥160 mmol/L, change baseline IV to 0.25% saline.
- Transfuse if hemoglobin is lower than 10 mg/dL.
- Adjust fraction of inspired oxygen and positive end-expiratory pressure to maintain PaO_2 >100 mmHg and oxygen saturation higher than 92%.
- Insert a Foley catheter. Measure fluid input and urine output and monitor urine specific gravity every 2 hours:
  - If the urine output over 2 hours is >500 mL with specific gravity of 1.005 or lower, begin treatment for neurogenic diabetes insipidus if not already on vasopressin infusion:
    - Administer *aqueous* pitressin 6–10 units IV push.
    - Start IV pitressin 2–4 U/h titrated to maintain SBP >100 mmHg and urine output <150 mL/h.
    - Replace hourly urine output milliliter for milliliter with D5W.
- Check the fingerstick glucose level every 2–4 hours:
  - If the fingerstick glucose level is >180 mg/dL, begin *insulin drip* (100 units regular insulin in 1000 mL 0.9% saline) starting at 20 mL/h (2 U/h), titrated to maintain blood glucose between 120 and 180 mg/dL.

Psychosocial issues

The emotional and psychosocial impact of death is always stressful for those who survive the patient; this can be even more difficult in the setting of brain death. Communicating the concept and meaning of brain death to the patient's family is paramount. This communication, however painful, should be initiated as early as possible in order to give those involved time to adjust to the situation. Although family permission is generally *not* required to discontinue life support once a patient is declared legally brain dead, their

consent and understanding is extremely important. Misunderstanding, bereavement, emotional upset, and religious or moral beliefs may lead family members to object to 'pulling the plug' in some cases. In these instances, third party mediation by a medical ethics consultant or member of the clergy may be desirable.

Special populations

Children

Diagnosing brain death in children includes the following:

- Coma and apnea must be present.
- Absence of brainstem function.
- No significant hypothermia or hypotension for age.
- Observation period by age:
  - Seven days to 2 months: two EEGs and exams separated by 48 hours.
  - Two months to 1 year: two EEGs and exams separated by 24 hours.
  - Older than 1 year: observation from 12 to 24 hours, shorter if EEG shows electrical silence.

Reading list

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Stevens RD, Bhardwaj A. Approach to the comatose patient. Crit Care Med 2006;34(1):31–41.

Widjicks EFM. Determining brain death. Continuum (Minneap Minn) 2015:21:1411–24.

Wijdicks EFM. Brain Death, 3rd edition. Oxford: Oxford University Press, 2017.

Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74(23):1911–18.

Suggested websites

https://www.aan.com/guidelines/

Guidelines

National society guidelines

Title	Source	Date and reference
Evidence-Based Guideline Update: Determining Brain Death in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology	American Academy of Neurology	2010 Neurology 2010;74(23):1911–18

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 32

Toxicology and Drug Reactions

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OVERALL BOTTOM LINE

- The hallmark of managing patients with drug toxicities is primarily to assess and treat compromises in airway, breathing, and circulation (the ABCs):
  - Intubate and mechanically ventilate patients with respiratory compromise.
  - Establish intravenous access, hydrate with intravenous fluids for hypotension.
  - Obtain labs to assess the underlying etiology of the compromise.
- Rapid assessment for quickly reversible causes of altered mental status, such as hypoglycemia, and opiate intoxication should be done; dextrose and naloxone 0.4 mg should be administered, respectively.
- Assess vital signs and physical exam findings that can help identify a toxidrome so that appropriate reversal medications and antidotes can be administered.
- Consider advanced therapies to block absorption of toxins or to enhance elimination.
- Educate and obtain psychiatric evaluations for patients after treating the acute ingestion so that future episodes can be minimized.

Background

Definition of disease

- Specific toxic syndromes or toxidromes are a symptom complex of a specific poisoning.
- Given the similarities of the pharmacology of many toxins, treatment can be tailored to various toxidromes based on clinical presentation.

Incidence/prevalence

- In its 2014 annual report, the American Association of Poison Control Centers compiled data from 56 poison centers in the USA, which reported a total of 2 165 142 human toxin exposure cases, 58% of which were adult exposures.
- The five substance classes most frequently involved in all human exposures were analgesics (11.3%), cosmetics/personal care products (7.7%), household cleaning substances (7.7%), sedatives/hypnotics/antipsychotics (5.9%), and antidepressants (4.4%).

Etiology

- The etiology of a poisoning is variable and can be from intentional drug overdose, illicit drug abuse, unintentional drug interactions, or environmental or occupational toxin exposures.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Prevention

Primary prevention

- Community, family, and school-based programs implemented in early childhood can help mitigate the risk of drug and alcohol abuse.
- Educate patients regarding safe use, storage, side effects, and interactions of all prescription and over-the-counter medications.

Secondary prevention

- Drug and alcohol rehabilitation as well as psychiatric evaluation should be considered when appropriate.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- History can be unreliable or incomplete when evaluating an intoxicated patient; however, accompanying friends, family, or patients' pharmacists can provide some insight.
- Treat all overdoses as polysubstance overdoses unless proven otherwise.
- Different toxidromes have specific vital sign and physical exam findings which can help identify the specific toxin or toxin class and guide the treatment.
- Pre-existing conditions can confound the presentation of a known toxidrome and should be taken into account when evaluating every patient.
- Toxins with specialized therapies such as salicylates, acetaminophen, and tricyclic antidepressants should be ruled out quickly with serum testing and ECG screening.
- Laboratory evaluation will include urine and serum assays that can help detect specific toxins, and labs to help assess for acid–base abnormality, anion gap, and osmole gap.

Differential diagnosis

It is important to consider alternative or coexisting conditions for altered mental status other than toxin and drug ingestion such as sepsis, stroke, and seizures.

Typical presentation

The typical presentation of an intoxicated patient involves altered mental status as well as alteration of vital signs and physical exam findings specific for each toxidrome. Detailed presentations of the different toxidromes and associated drugs are listed in Table 32.1.

Clinical diagnosis

History

- A history from an altered patient is usually unreliable. Efforts should be made to obtain the types and quantities of prescribed, over-the-counter, or illicit drugs that the patient may have ingested.
- Emergency responders, friends, family members, and outpatient pharmacists can help provide information.

Physical examination:

See Table 32.1 for the typical presentations and different physical exam findings for different toxidromes.

Useful clinical decision rules and calculators

- The Rumack–Matthew nomogram for acetaminophen ingestion uses time from ingestion and acetaminophen level to determine if *N*-acetylcysteine should be administered (https://www.mdcalc.com/acetaminophen-overdose-nac-dosing).

Table 32.1 Presentation of common toxidromes.

Toxidrome	Temp	BP/ HR	Resp rate	Mental status	Pupils	Mucous membranes	Ref-lexes	Other common findings	Associated drugs/toxins
Anticho-linergic	↑	↑	↕	Delirium	Mydriasis	Dry	–	'Hot as a hare, dry as a bone, red as a beet, mad as a hatter, blind as a bat'	Antihistamines Atropine Benztropine TCA Scopolamine Phenothiazines
Cholinergic	–	↕	↑–	Variable	Miosis	Wet	–	SLUDGE: salivation, lacrimation, urination, defecation, GI diarrhea, emesis, bronchorrhea	Organophosp-hates Carbamates Physostigmine Pilocarpine Edrophonium Nicotine alkaloids
Neuroleptic malignant syndrome	↑	↕	↑–	Variable	–	Diaphoretic	↑	Lead pipe rigidity, bradykinesia	Haloperidol Phenothiazines Risperidone Olanzapine Chlorpromazine
Opiate	↓–	↓–	↓↓	Decreased LOC	Miosis	–	↓–	Respiratory arrest	Heroin Morphine Fentanyl Methadone Meperidine
Sedative-hypnotic	↓–	↓–	↓–	Decreased LOC	Miosis to no change	–	↓–	Respiratory arrest	Benzodiazepines Alcohols Barbiturates
Serotonin syndrome	↑–	↑	↑–	Variable	Mydriasis	Diaphoretic	↑↑	Tremor, shivering, diarrhea, clonus, lower extremity rigidity	Antidepressants Meperidine Trazadone Triptans
Sympatho-mimetic	↑	↑	↑	Activating	Mydriasis	Diaphoretic	↑	Hypokalemia, metabolic acidosis, agitation, hallucinations	Cocaine Amphetamines Ephedrine Pseudoephed-rine Theophylline

Laboratory diagnosis

List of diagnostic tests

- Initial laboratory tests should include a comprehensive metabolic panel, complete blood count, and arterial blood gas. Serum levels of acetaminophen, salicylates, and ethanol should be assessed.

- Serum and urine drug assays can help identify exposures to different drugs or their metabolites but cannot confirm that they are the reason for the poisoning. It is important to identify the specific toxin through history, physical exam, and clinical toxidrome and use these assays as validating tests.
- The serum anion gap, osmolal gap, and oxygen saturation gap can help narrow down specific toxins:
  - Serum anion gap = $[Na^+] - ([Cl^-] + [HCO_3^-])$.
    - An elevated serum anion gap of >12 mEq/L is usually seen with ingestions of salicylates, methanol, ethylene glycol, isoniazid, paraldehyde, formaldehyde, NSAIDs, and metformin.
    - A low serum anion gap of <7 mEq/L is seen with ingestion of lithium.
  - An osmolal gap reflects the presence of an osmotically active substance, usually an alcohol, that has been ingested. It is the difference between the measured and the calculated osmolality of a serum.
    - Calculated osmolality ($Osm_{calculated}$) = 2[Na^+ (mmol/L)] + [urea (mg/dL)]/2.8 + [glucose (mg/dL)]/18 + [ethanol (mg/dL)]/4.6.
    - Osmolal gap (normal <10) = $Osm_{measured} - Osm_{calculated}$.
    - Causes of an elevated osmolal gap are acetone, isopropanol, mannitol, methanol, ethylene glycol, formaldehyde, and paraldehyde.
  - Winter's formula can be used to calculate the expected PCO_2 compensation in a pure metabolic acidosis.
    - $PCO_2 = 1.5 \times HCO_3 + 8 \pm 2$.
    - It identifies a mixed acid–base disorder, often a respiratory acidosis, reflecting inadequate respiratory compensation for the metabolic acidosis. This signifies the patient's need for non-invasive or invasive positive pressure ventilation.
    - Salicylate toxicity usually produces a mixed metabolic acidosis and respiratory alkalosis.
  - The oxygen saturation gap is the difference between the percentage oxygen saturation on an arterial blood gas and the percentage saturation measured by multi-wavelength co-oximetry.
    - The oxygen saturation gap is usually elevated from the presence of carboxyhemoglobin, methemoglobin, or sulfhemoglobin.
    - Cyanide poisoning does not result in an elevated oxygen saturation gap.

List of imaging techniques

- Imaging techniques should be guided by clinical presentation and physical examination; this can include brain imaging for altered mental status and chest imaging for hypoxemia or respiratory insufficiency.
- Abdominal X-rays may help in certain toxicities, such as body packers, ingestion of radio-opaque iron pills or leaded foreign bodies, and caustic ingestions.

Potential pitfalls/common errors made regarding diagnosis of disease

- It is important to consider complications related to toxin ingestion as well as coexisting conditions when treating patients. For example, patients can come in with both an acute MI as well as cocaine intoxication and both should be treated appropriately.
- Some drug assays may result in false positive results, false negative results, or reflect the patient's drug exposure rather than the drug poisoning. History, physical exam, and clinical toxidrome must be used to diagnose and treat the drug poisoning.
- All intentional drug overdoses should be screened for an acetaminophen concentration since it is a common ingestion, it may not be disclosed in the history, and there is no clinical toxidrome to identify the acute ingestion.
- Be aware that several newer synthetic drugs such as synthetic cannabinoids and bath salts can have a varied presentation depending on their composition.

Treatment

Treatment rationale

- Initial treatment of all toxin ingestions should focus on managing airway, breathing, circulation, and neurologic deficits (the ABCDs) of toxicology.
- Reverse the toxin if possible with specific antidotes (Table 32.2).
- Consider therapies that will reduce absorption (GI decontamination) or enhance elimination (urine alkalization, hemodialysis, intravenous lipid emulsion):
  - Activated charcoal is most effective within 1–2 hours of ingestion and can help reduce GI absorption by binding the toxin. Activated charcoal is not recommended in heavy metals, caustic agents, hydrocarbon, and toxic alcohol ingestion. Multiple-dose activated charcoal is most effective for ingestions with theophylline, quinine, carbamazepine, dapsone, and phenobarbital, among others. It is contraindicated in patients at risk for bowel obstruction or perforation, or at risk of aspiration due to vomiting, altered mental status, or an unprotected airway.
  - Whole bowel irrigation is used for lithium, iron, sustained-release or enteric-coated medication overdose, or in cases of body packing. It is contraindicated with bowel obstruction, perforation, ileus, nausea/vomiting, or an unprotected airway.
  - Routine use of gastric lavage or induced emesis is not recommended.
  - Once toxin reversal and elimination have been attempted, supportive care should be the basis of treatment.

When to hospitalize

Patient who present with acute intoxication should be hospitalized or placed under observation for monitoring since the severity of ingestion can be unknown at the time of presentation.

Table of treatment

Toxin	Treatment and antidotes
Acetaminophen	*N*-acetylcysteine: • PO: 140 mg/kg load then 70 mg/kg every 4 hours × 17 doses • IV: 150 mg/kg over 60 minutes; then 50 mg/kg over 4 hours; then 100 mg/kg over 16 hours Treatment should not be delayed while waiting for levels if known acetaminophen ingestion Rumack–Matthew nomogram uses time from ingestion and the acetaminophen level to determine if *N*-acetylcysteine is necessary Referral to liver transplant center if patient is at risk for developing fulminant hepatic failure Potential list for transplant according to King's College Criteria: • Arterial pH <7.3 after adequate fluid resuscitation *OR* • Creatinine >3.4 mg/dL, INR> 6.5, and grade III hepatic encephalopathy or worse within 24 hour period
Anticholinergics	Physostigmine 0.5–2 mg IV over 5 minutes May repeat in 5–10 minutes

(*Continued*)

(*Continued*)

Toxin	Treatment and antidotes
Benzodiazepines	Flumazenil 0.2 mg IV over 2 minutes Repeat 0.2 mg dose at 1 minute intervals to desired level of consciousness (max. dose 1 mg) Caution with patient on chronic benzodiazepines as flumazenil can precipitate withdrawal or possible seizures
Beta-blockers	Glucagon 5–10 mg IV bolus over 1 minute then infusion of 1–10 mg/h titrated to symptom response Consider cardiac pacing Hyperinsulinemia–euglycemia therapy: • Insulin 1 U/kg IV bolus • Then, 0.5–1 U/kg/h IV drip • Monitor glucose every 30 minutes • If BG ≤250, give dextrose 25–50 g IV bolus then 0.5 g/kg/h IV infusion • Monitor potassium for hypokalemia
Botulinum	Botulinum antitoxin 1 vial IV; repeat every 2–4 hours PRN Epinephrine at bedside
Calcium channel blockers	2–3 g calcium gluconate or 1 g calcium chloride every 10 minutes Monitor serum calcium for hypercalcemia Glucagon 5–10 mg IV bolus over 1 minute then infusion of 1–10 mg/h can reduce vasopressor requirements Hyperinsulinemia–euglycemia therapy: • Insulin 1 U/kg IV bolus • Then, 0.5–1 U/kg/h IV drip • Monitor glucose every 30 minutes • If BG ≤250, give dextrose 25–50 g IV bolus then 0.5 g/kg/h IV infusion • Monitor potassium for hypokalemia
Carbon monoxide	100% supplemental O_2 with 4.5–4.8% CO_2 Hyperbaric O_2 therapy for severe symptoms such as COHgb ≥25% (≥15% in pregnancy), coma, syncope, altered mental status, seizure, fetal distress, myocardial ischemia
Cocaine	Supportive therapy: • Benzodiazepines for agitation • Active and passive cooling for hyperthermia • Calcium channel blockers and nitrates for hypertension
Cyanide	100% oxygen Amyl nitrate 1 amp inhalation for 15–30 seconds every 30 seconds Sodium thiosulfate 12.5 g IV over 10–30 minutes; can repeat half dose in 2 hours or if symptoms reappear Hydroxycobalamin 5 g IV over 30 minutes Sodium nitrite 300 mg IV over 3 minutes; can repeat half dose if symptoms reappear
Digoxin	Digibind or digifab Acute ingestion: 10 vials: • No. of vials = [amount ingested (mg)] × 0.8/0.5 mg Chronic ingestion: 3–6 vials: • No. of vials = [digoxin level (ng/mL)] × [weight (kg)]/100

Toxin	Treatment and antidotes
Ethylene glycol	Goal: treat until levels <20 mg/dL: • Fomepizole 15 mg/kg IV load over 30 minutes, then 10 mg/kg IV every 12 hours × 4 doses • Continue 15 mg/kg IV bolus every 12 hours as needed Thiamine 50–100 mg daily Pyridoxine 100 mg daily Hemodialysis in severe organ dysfunction Ethanol infusion (less preferred)
Iron	Deferoxamine 5 mg/kg/h IV and titrate to 15 mg/kg/h IV; max. dose 68 g. Limit to 24 hours
Isoniazid	Pyridoxine 1 g IV for every gram of isoniazid For unknown quantities, 5 g IV at 0.5 g/min until seizures stop
Lead	Succimer 10 mg/kg PO every 8 hours × 5 days; then 10 mg/kg PO every 12 hours × 14 days For lead encephalopathy: • Dimercaprol 75 mg/m^2 deep IM every 4 hours x 5 days; first dose precedes EDTA by 4 hours • Followed by edetate calcium disodium 1500 mg/m^2/day continuous IV or IM divided twice to four times a day
Lithium	Renal replacement therapy for serum lithium levels >3.5 mEq/L in acute ingestion and >2.5 mEq/L in chronic ingestion Monitor for rebound increase in lithium levels when using hemodialysis as it does not affect intracellular lithium
Methanol	Goal: treat until levels <25 mg/dL: • Fomepizole 15 mg/kg IV loading dose over 30 minutes, then 10 mg/kg IV bolus every 12 hours × 48 hours • Followed by 15 mg/kg IV bolus every 12 hours as needed Folate 1–2 mg/kg (50–75 mg) IV every 4 hours × 24 hours. Extra dose at completion of hemodialysis Hemodialysis in severe organ dysfunction or levels >50 mg/dL Ethanol infusion (less preferred)
Methemoglobinemia	Methylene blue 1–2 mg/kg or 0.1–0.2 mL/kg of 1% solution over 5 minutes
Neuroleptic malignant syndrome	Bromocriptine 2.5–10 mg PO three to four times a day
Opiates	Naloxone 0.04–0.05 mg IV initial dose, can increase to 1–2 mg IV if no response after 2–3 minutes to max. dose of 10 mg If repeated boluses are required, consider naloxone infusion with hourly rate two-thirds of IV bolus dose given Goal: adequate ventilation or respiratory rate ≥12. Do not titrate to normal level of consciousness Caution in patients with chronic opiate use as high doses of naloxone can induce withdrawal

(*Continued*)

(*Continued*)

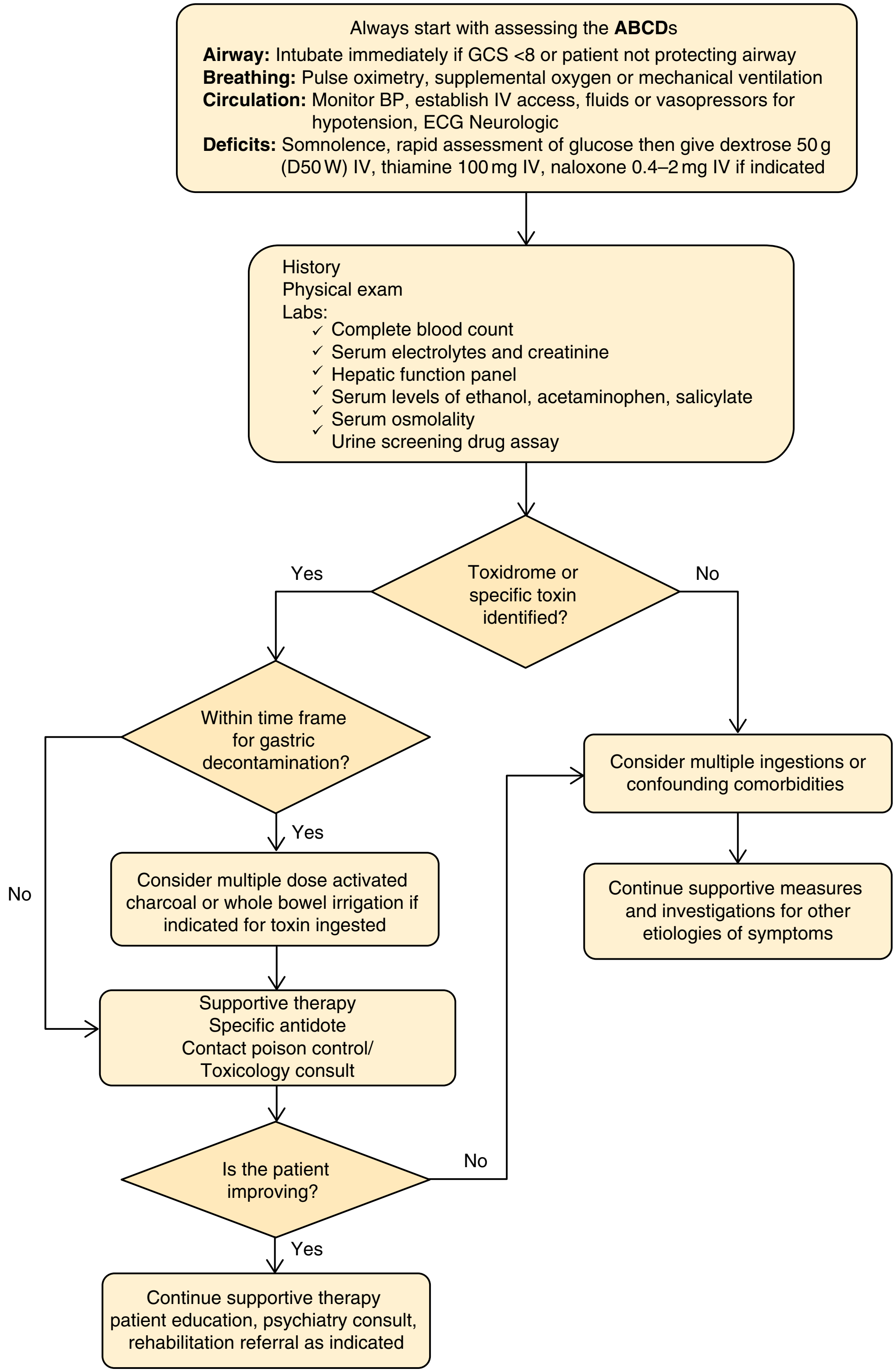
Toxin	Treatment and antidotes
Organophosphates/ cholinergic toxidrome	For respiratory symptoms the goal is atropinization (mydriasis, dry mouth, tachycardia): atropine 1–2 mg IV push initially with subsequent doses doubled every 2–3 minutes until symptoms resolve Glycopyrrolate 1–2 mg IV if atropine dose required is high enough to cause additional CNS toxicity For severe toxicity, muscle fasciculation, and weakness: pralidoxime 1–2 g or 25–50 mg/kg IV over 30 minutes, then 200–500 mg/h or 10–20 mg/kg/h infusion Benzodiazepines such as diazepam 10–20 mg IV can be used for seizures, anxiety, or fasciculation
Salicylates	Multiple dose activated charcoal $NaHCO_3$ 150 mEq in 1 L D5W IV infusion: goal is urine pH to 8.1 or plasma pH 7.45–7.50 Hemodialysis: • Acute ingestion: serum salicylate level >120 mg/dL or levels >100 mg/dL 6 hours post-ingestion • Chronic ingestion: serum salicylate level >60 mg/dL or for symptomatic patient
Serotonin toxidrome	Cyproheptidine 4–12 mg PO initial dose then 2 mg every 2 hours until clinical response Maintenance dose 4–8 mg every 6 hours (max. 32 mg/day)
Sulfonylureas	25 g of 50% dextrose (D50W) IV Octreotide 50–150 μg IM/SQ every 6 hours
Tricyclic antidepressants	$NaHCO_3$ 1–2 mEq/kg IV bolus for QRS widening $NaHCO_3$ 150 mEq in 1 L D5W IV at 1–3 mEq/mg/h to target serum pH 7.45–7.50 Lidocaine for ventricular arrhythmias 200 mL of 3% NaCl hypertonic saline for refractory arrhythmias despite pH >7.55
Valproic acid	L-carnitine: • Symptomatic: 100 mg/kg IV (max. 6 g) load over 30 minutes; then 15 mg/kg IV every 4 hours over 10–30 minutes • Asymptomatic: 100 mg/kg/day (max. 3 g) PO divided over 6 hours

Prevention/management of complications

- Some patients presenting with severe intoxications can require prolonged ventilation or ICU support. It is important to ensure that measures be taken to avoid complications related to supportive therapy, such as minimizing sedation, providing daily spontaneous awakening trials, and mobilizing patients.
- Once the patient is recovering, psychiatric evaluation is necessary for intentional ingestions, and drug and alcohol rehabilitation should be considered to prevent readmissions and relapse.

Management/treatment algorithm (Algorithm 32.1)

Algorithm 32.1 Managing the hospitalized overdose patient



CLINICAL PEARLS

- Always remember to manage the airway, breathing, circulation, and neurologic deficits of the intoxicated patient.
- Consider multiple ingestions of different toxins when treating patients and administer antidotes to known toxins.
- There can be confounding comorbid illnesses along with the acute intoxication, such as myocardial infarctions in patients using cardiotoxic medications or sepsis and bacteremia in patients using intravenous drugs.
- It is important to follow-up after treating an acute intoxication with patient education, psychiatric evaluation, or drug and alcohol rehabilitation when applicable.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- The prognosis depends on the type of ingestion and organ system primarily affected.
- For example, some patients with fulminant liver failure from acetaminophen ingestion or from drug-induced liver disease may require liver transplantation for survival.
- Most patients with unintentional ingestions recover when provided the appropriate supportive care.

Reading list

Brooks DE, et al. Toxicology in the ICU, Part 2: specific toxins. Chest 2011;140:1072–85.

Fertel BS, Nelson LS, Goldfard DS. Extracorporeal removal techniques for the poisoned patient: a review for the intensivist. J Intensive Care Med 2010;25:139–48.

Levine M, et al. Toxicology in the ICU, Part 1: general overview and approach to treatment. Chest 2011;140:795–806.

Mokhlesi B, et al. Adult toxicology in critical care: Part I: general approach to the intoxicated patient. Chest 2003;123;577–92.

Mokhlesi B, et al. Adult toxicology in critical care: Part II: specific poisonings. Chest 2003;123;897–922.

Suggested websites

http://www.acmt.net

https://www.clintox.org

http://www.extrip-workgroup.org

www.poison.org

Guidelines

National society guidelines

Title	Source and comment	Date and weblink
ACMT Position Statements	American College of Medical Toxicology Position Statements The ACMT provides position statements intended to summarize a vast body of reviewed literature and expert opinion with references	2016 http://www.acmt.net/resources_position.html

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

with website

PART 5

Surgical Critical Care

Section Editor: Adel Basilly-Marcus

CHAPTER 33

Gastrointestinal Bleeding

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OVERALL BOTTOM LINE

- Greater than 80% of gastrointestinal (GI) bleeds stop spontaneously.
- Upper GI bleeds proximal to the ligament of Treitz are most frequently due to peptic ulcer disease, while lower GI bleeds distal to the ligament of Treitz are most commonly due to diverticulosis.
- With a suspected upper GI bleed, proton pump inhibitors (PPIs) should be started on presentation to prevent GI bleeding; beta-blockers should be used as primary prophylaxis of bleeding from varices.
- Early upper endoscopy surveillance of upper GI ulcers and detection and treatment of *Helicobacter pylori* causes a reduction GI bleeds.
- Limiting exposure to antiplatelet and anticoagulant agents as appropriate reduces GI bleeding episodes.

Background

Definition of disease

- Bleeding that originates anywhere in the GI tract and may manifest as hematemesis, hematochezia, melena, or maroon-colored stools.

Disease classification

- Upper GI bleeding originates proximal to the ligament of Treitz, whereas lower GI bleeding originates distal to the ligament of Treitz.

Incidence/prevalence

- The incidence of acute upper GI bleeding is 50–100 per 100 000 persons per year in the USA.
- The incidence of lower GI bleeding is 20 cases per 100 000 individuals per year.

Etiology

- The most common cause of acute upper GI hemorrhage is peptic ulcer disease. Additional causes include but are not limited to non-steroidal anti-inflammatory (NSAID) use, stress gastritis, gastroesophageal varices, and Mallory–Weiss tears.
- The most common causes of lower GI bleed include diverticulosis (24–47%), colitis (6–36%), neoplasms (9–17%), and angiodysplasia (2–12%).

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Pathology/pathogenesis

- Upper GI bleeding:
  - Duodenal ulcers occur more frequently than gastric ulcers and bleeding may occur with ulcerative erosion through the posterior wall into the gastroduodenal artery, resulting in hemorrhage or hematemesis.
  - NSAID use is also associated with mucosal injury that may result in ulcerative disease causing acute upper GI hemorrhage.
  - Stress gastritis as a cause of upper GI bleeds results from superficial gastric ulcers due to altered gastric mucosal blood flow and impaired clearance of hydrogen ions from the mucosa.
  - Gastroesophageal varices may cause upper GI bleeding in cirrhotic patients.
  - Dieulafoy vascular malformations are generally due to unusual large arteries running through the gastric submucosa which may result in bleeding due to gastric erosion.
- Lower GI bleeding:
  - The most common cause of lower GI bleeding is diverticulosis. Bleeding from diverticulosis results from a perforated vasa recta at the neck or apex of a diverticulum.
  - Colonic angiodysplasia arises from age-related degeneration of previously normal intestinal submucosal veins and overlying mucosal capillaries.
  - Ischemic colitis is due to impaired local microvascular perfusion of the colonic wall.

Predictive/risk factors

Risk factor	Odds ratio
Aspirin 81 mg	1.8
NSAID	1.4
Aspirin plus NSAIDs	3.6
Coagulopathy	4.3
Aspirin plus antiplatelet	6.7
Respiratory failure/mechanical ventilation	15.6

Prevention

BOTTOM LINE/CLINICAL PEARLS

- PPIs are protective and have been shown to decrease rebleeding. PPIs should be started when upper GI bleeding is suspected.
- *H. pylori* treatment, if indicated, should be initiated and decreases bleeding risks.
- Beta-blockers and prophylactic antibiotics should be started to reduce the risk of variceal bleeding in cirrhotic patients.
- Antiplatelet, anticoagulant agents, and NSAIDs should be limited as appropriate to prevent or minimize GI bleeds.

Screening

- Patients with gastric and duodenal ulcers should have screening biopsies obtained for *H. pylori*. Patients who test positive should be treated.

Primary prevention

- With suspected upper GI bleeds, PPIs should be started on presentation until the cause of bleeding is confirmed. PPIs should be used as stress ulcer prophylaxis in critically ill patients to prevent GI bleeding.
- The risk of ulcer formation in patients taking NSAIDs is significantly reduced with prophylactic use of PPI or histamine-2 (H_2) receptor antagonists. PPIs are more effective in protecting patients on NSAIDs than H_2 receptor blockers.
- Beta-blockers can be used for primary prophylaxis of bleeding from varices. Beta-blockers have a 9% absolute risk reduction of GI bleeding episodes.
- Endoscopic surveillance of upper GI ulcers and detection and treatment of *H. pylori* leads to a reduction in GI bleeds.
- Decreasing the use of antiplatelet and anticoagulant agents as appropriate reduces GI bleeding episodes.

Secondary prevention

- PPIs should be used over H_2 blockers to reduce rebleeding episodes after successful endoscopic therapy. PPIs may promote hemostasis via neutralization of gastric acid leading to stabilization of blood clots. PPI therapy decreases rebleeding rate, in addition to decreasing the length of hospital stay and blood transfusion needed.
- Beta-blockers have a 21% absolute risk reduction of recurrent GI bleeds.
- Endoscopic treatments can prevent rebleeding. Specifically, endoscopy plus prophylactic treatment of varices decrease bleeding risk. Banding ligation is superior to injection sclerotherapy treatment and beta-blockers alone. Endoscopy plus PPI treatment has a lower risk of rebleeding than PPI treatment alone (11.6% risk of bleed versus 1.1%).
- Treatment for *H. pylori* if indicated helps reduce the recurrence of GI bleeding compared with no treatment or chronic antisecretory treatment alone.
- Somatostatin analogs like octreotide and prophylactic antibiotics in cirrhotic patients can reduce rebleeding from variceal causes.

Diagnosis

Typical presentation

- Upper GI bleeding may present as hematemesis or melena (dark or tarry black stool); lower GI bleeding may present as hematochezia (maroon stool, bright red blood per rectum).
- Hematemesis and melena are generally indicative of a bleeding source proximal to the ligament of Treitz. Frank hematemesis is of greater clinical concern, whereas coffee ground emesis may be indicative of a more limited upper GI bleed.
- Melena occurs due to a source proximal to the ligament of Treitz (90%), oropharynx, small bowel, or colon. May see bloody aspirate on nasogastric lavage or identify source via upper endoscopy.
- Hematochezia may present secondary to a massive upper GI bleed which may result in orthostatic hypotension or due to lower GI bleed. A lower source may be supported by a negative nasogastric aspirate and a bleeding scan or colonoscopy.

Clinical diagnosis

History

- When taking a history, it is important to elicit the patient's general medical history to understand their comorbidities as well as an accurate medication history. Specifically, a history of epigastric pain with NSAID use may lead one to think of peptic ulcerative disease as a source of GI bleed.
- A recent history of vomiting and retching with associated hematemesis may be secondary to Mallory–Weiss.
- A history of alcohol use may suggest gastroesophageal variceal bleed or portal hypertension.
- In patients who have had an aortic graft repair an aorto-enteric fistula should be ruled out.
- Weight loss in a smoker with vague abdominal pain and dysphagia may point to a malignancy.

- A history of medical comorbidities including renal or hepatic dysfunction are important in identifying coagulopathies. A medication history including use of NSAIDs or antiplatelet or anticoagulant agents is important in planning patient resuscitation and treatment.

Physical examination

- The physical exam should begin with an examination of the patient's general status. A patient who is obtunded, tachypneic, tachycardic, and diaphoretic is of great concern and resuscitation should be initiated immediately.
- Orthostatic hypotension is indicative of a 15% blood volume loss and supine hypotension may indicate a 40% blood volume loss. Additionally, one should inspect the patient for signs of anemia including cool, clammy, mottled, or pale skin or mucous membranes.
- An examination of the abdomen may demonstrate epigastric abdominal pain consistent with peptic ulcer disease versus peritoneal signs consistent with a possible perforated viscus.
- A rectal exam should be performed to identify any obvious source of distal rectal bleed including hemorrhoids or fissures.

Useful clinical decision rules and calculators

- The International Consensus Upper Gastrointestinal Bleeding Conference Group recommends using mortality risk stratification tools. Two scoring systems used for GI bleeding include the Rockall score and the Blatchford score.
- The Rockall score (www.mdcalc.com/rockall-score-upper-gi-bleeding-complete) incorporates age, shock, comorbidity, diagnosis, and endoscopic stigmata of recent hemorrhage (range 0–11). Although validated for risk stratification, the Rockall score also predicts recurrent bleeding. Rebleeding occurred in <5% of patients, with mortality 0–0.2% among patients with scores 0–2. For scores ≥5 one-fourth to one-half of patients experienced a rebleed.
- The Glasgow Blatchford score (www.mdcalc.com/glasgow-blatchford-bleeding-score-gbs) can be calculated on patient presentation since no endoscopic information is required. The Blatchford score incorporates the blood urea nitrogen, hemoglobin, systolic blood pressure, pulse, and presence of melena, syncope, hepatic disease, and/or cardiac failure. The score ranges from 0 to 23 with an increasing score having a greater association with need for urgent endoscopic intervention. The modified Blatchford was found to outperform the Rockall score and full Blatchford score in regard to predicting the need for clinical intervention, rebleeding, and mortality.
- The AIMS65 score (www.mdcalc.com/aims65-score-upper-gi-bleeding-mortality) also uses data available prior to endoscopy and has a high accuracy for predicting inpatient mortality among upper GI bleed patients.

Laboratory diagnosis

List of diagnostic tests

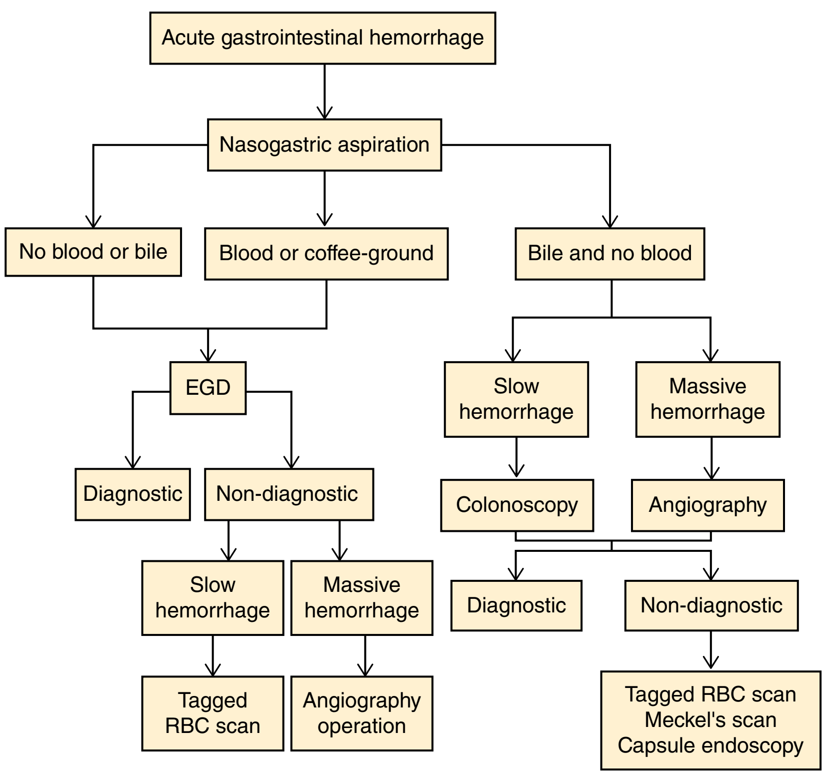
- Patients presenting with GI bleeds should be evaluated with routine labs including CBC and chemistries to evaluate for anemia and resuscitation status. Additionally, liver function tests, a coagulation panel, and type and cross should be obtained to assess the patient's coagulopathy and to prepare for blood transfusion if necessary.
- An ECG and cardiac enzymes should be obtained in patients who have sustained a sizeable blood loss or have resultant hypotension particularly in the face of a cardiac history in order to evaluate for ischemic cardiomyopathy.
- A nasogastric (NG) tube can provide a simple diagnostic test to differentiate upper and lower GI bleeding since it is inexpensive and safe with a sensitivity of 42% and specificity of 91%. The NG tube should be placed and lavaged. Bloody output identifies a likely source of upper GI bleed and has been shown to result in a shorter time to endoscopy. Clear output is equivocal and requires further investigation, whereas non-bloody bilious output suggests no upper GI bleed.

List of imaging techniques

- Upper endoscopy is the diagnostic modality of choice for acute upper GI bleed with a high sensitivity and specificity for localizing bleeding, and can be utilized for treatment as well. Colonoscopy should be completed if hematochezia or melena are found in a patient with a negative upper endoscopy.
- Technetium-99m sulfur colloid allows for detection of GI bleeding at rates from 0.1 to 0.5 mL/min. For sulfur colloid scans, the patient must be actively bleeding during the limited time the label is present. With technetium labeling of RBCs, greater sensitivity for detection of GI bleeding was noted. With this mode, patients with intermittent bleeding can be scanned several times over a 24 hour period. The anatomic accuracy for tagged RBC scans is 70–85%, and it may serve as a screening for angiography.
- CT angiography serves as a fast, widely available, and minimally invasive diagnostic tool that detects bleeding at rates of 0.3–0.5 mL/min. A sensitivity of 85% and specificity of 92% were reported in a meta-analysis of 22 studies. The study found greater precision when it came to localizing the site of bleeding. CT angiography, however, lacks therapeutic capability, requires radiation exposure, and utilizes intravenous contrast, which can cause allergic reactions or nephropathy.
- Angiography requires a rate of active blood loss of 0.5–1.0 mL/min. Negative arteriograms can be reduced with screening radionuclide imaging. If no prior localization exists, the superior mesenteric artery is examined first, followed by the inferior mesenteric or celiac vessels with success rates of 25–70%. Angiography does not require bowel preparation and provides accurate anatomic location in addition to potential therapeutic intervention with transcatheter embolization techniques.

Diagnostic algorithm (Algorithm 33.1)

Algorithm 33.1 Investigations in acute gastrointestinal hemorrhage



Potential pitfalls/common errors made regarding diagnosis of disease

- Radionuclide scanning with sulfur colloid or tagged RBCs and CT angiographic diagnostic imaging techniques require active bleeding at the time of diagnosis. Most GI bleeding stops spontaneously and thus if the bleeding has ceased, localization is difficult to achieve. Additionally, to localize with the sulfur colloid label the patient must be actively bleeding in the few minutes the label is present, while for a tagged RBC study the patient may be intermittently scanned for 24 hours in order to localize the lesion.
- The accuracy rates for radionuclide studies are incredibly variable with accuracy ranging from 24% to 91%. The difficulty localizing the bleeding lesion is based on the need for active bleeding as well as complicating factors such as a redundant bleeding left colon appearing as a right-sided GI bleed.

Treatment

CLINICAL PEARLS

- Most GI bleeding will stop spontaneously. Non-operative medical management should be initiated first.
- Patients should be evaluated and triaged appropriately with early initiation of appropriate resuscitation, medical management, endoscopy, and localization of the bleed.
- Early endoscopy and colonoscopy as well as imaging is essential to early localizing of the bleeding lesion in order to implement proper treatment if bleeding does not cease on its own. Repeat endoscopy is generally preferable in stable patients to surgical treatment.
- Hemodynamically unstable patients or patients with persistent bleeding are more likely to require surgical management of GI bleeding.

Treatment rationale

- If an upper GI bleed is suspected, antiplatelet and anticoagulant agents and NSAID use should be stopped as appropriate.
- Acid suppression with PPIs is the hallmark of treatment for ulcer-related bleeding.
- Endoscopy should be performed for diagnostic information as well as therapeutic potential. Erythromycin before endoscopy improves visualization during endoscopy.
- Ulcers should be biopsied and patients treated for *H. pylori* as appropriate. Active bleeding ulcers or ulcers with visible vessels may be treated with epinephrine injection, laser therapy, or heater probes. Hemoclips are an alternative to heater probes. Clips are mechanical devices that grasp the vessel and tissue; the clip does not cause tissue injury. Clips are useful for acute bleeding ulcers and may be used for Mallory–Weiss tears and Dieulafoy lesions.
- For hemodynamically unstable patients or persistent refractory hemorrhage, surgical options should be employed. Favorably located ulcers may be excised while others may be oversewn through gastrostomy or duodenotomy.
- For gastroesophageal variceal bleeding, beta-blockers should be initiated; endoscopic banding is superior to injection sclerotherapy.
- Lower GI bleeding should be evaluated with colonoscopy after a full colonoscopic prep. Endoscopically, bleeds may be treated with monopolar electrocoagulation, endoscopic injection sclerotherapy, contact probes, and lasers.
- Angiography may be used in patients with massive hemorrhage and may help in identifying and treating bleeds via transcatheter embolization. Attempts should be made to localize bleeding lesions and patients with persistent bleeding or instability should undergo segmental resection versus a subtotal colon resection.

When to hospitalize

- When evaluating patients using the Glasgow Blatchford score patients with a score of 0 can be managed as an outpatient.
- Patients with tachycardia, tachypnea, or hemodynamic instability should be transferred to a higher level of care.

Managing the hospitalized patient

- Patients should be evaluated on their initial presentation and triaged appropriately. Unstable patients should be admitted to the ICU with pulse oximetry and cardiac monitoring. Two large bore IVs (16 gauge or larger) should be placed and fluid resuscitation initiated with the patient made NPO.
- Patients should be resuscitated with normal saline or lactated Ringer's solution, and transfused with blood to achieve a Hg of <7 g/dL (70 g/L) or <9 g/dL for patients with increased risk of adverse events or unstable coronary artery disease.
- Patients with active bleeding and hypovolemia should receive a blood transfusion even if they have a normal hemoglobin. Patients with active bleeding with a platelet count <50 000 μL or INR >1.5 should be transfused platelets and fresh frozen plasma, respectively.

Table of treatment

Treatment	Comments
Conservative	Greater than 80% of GI bleeds stop spontaneously. Stable patients with low grading scores may be managed with supportive care
Medical: • Omeprazole (80 mg IV bolus followed by 8 mg/h infusion for 48–72 hours followed by 40 mg IV twice daily) • Sucralafate (1 g four times daily) • Octreotide (20–50 μg IV bolus followed by 20–50 μg/h IV)	Omeprazole was found to decrease rebleeding with no difference in mortality or blood transfusions Omeprazole and other PPIs were found to be superior to H_2 receptor blockers Octreotide can be used to slow a variceal bleed until definitive endoscopic therapy
Surgical	Patients with hemodynamic instability or unremitting bleed should undergo surgery to localize the GI bleed Upper GI bleeding may require ulcer resection with acid-reducing intervention versus gastrostomy versus duodenotomy with oversewing a bleeding vessel Lower GI bleeds can be treated with segmental resection
Radiologic	Angiography should be used for patients with massive hemorrhage. The bleed is identified with transcatheter embolization.

Prevention/management of complications

- Complications that may be encountered with the treatment of GI bleeds may occur most often with angiography.
- Angiography may cause contrast-induced nephropathy.
- Transcatheter embolization may result in arterial injury, thrombus formation, renal failure, or ischemic infarction. Super-selective embolization may help limit this complication but is associated with a risk of intestinal infarction of up to 20%.
- Such complications should be managed with supportive care and trending appropriate labs including lactate levels. Patients with true intestinal infarction will require segmental resection.

Special populations

Children

- GI bleeding in children should raise suspicion of a Meckel's diverticulum. This may be diagnosed with a Meckel's scan. Treatment involves resection of the Meckel's diverticulum and adjacent involved bowel.

Elderly

- Treatment for elderly patients is the same as for younger adults.

Prognosis

> **BOTTOM LINE/CLINICAL PEARLS**
> - More than 80% of GI bleeds stop spontaneously with a lower transfusion requirement associated with a higher rate of spontaneous cessation of bleeding.
> - Factors associated with rebleeding include hemodynamic instability, hemoglobin <10 g/L, active bleeding during endoscopy, large ulcer size (1–3 cm), ulcer location (posterior duodenal bulb, high lesser gastric curvature).
> - Risk calculators may help to quantify a patient's bleeding risk.

Natural history of untreated disease

- More than 80% of GI bleeds stop spontaneously; >99% of bleeding stopped in patients receiving <4 units of PRBCs per 24 hours.
- Factors associated with rebleeding include hemodynamic instability, hemoglobin <10 g/L, active bleeding during endoscopy, large ulcer size (1–3 cm), ulcer location (posterior duodenal bulb, high lesser gastric curvature).
- Patients with a Rockall score of 0–2 had <5% risk of rebleeding and mortality of 0–0.2%. A score of 5–8+ was associated with rebleeding in one-fourth to one-half of patients and a mortality of 11–41%

Prognosis for treated patients

- The all-cause mortality for upper GI bleeds is 6–10% despite treatment, with a mortality of 50% for variceal bleeding.
- Endoscopic therapy of bleeding ulcers resulted in a relative reduction of 69% in recurrent bleeding, 62% in emergent surgery, and 30% mortality with the greatest benefit seen in actively bleeding ulcers and ulcers with non-bleeding visible vessels.
- About 10% of bleeding diverticuli patients require operative intervention. A 3 year review demonstrated a 63% success rate in controlling colonic hemorrhage, with rebleeding in 16%. Subtotal colon resection resulted in morbidity in 20-42% and mortality in 17–33% due to sepsis or anastomotic leak.

Follow-up tests and monitoring

- Follow-up tests and monitoring should be tailored to the etiology of the GI bleed and further symptoms.
- Follow-up endoscopy or colonoscopy may be warranted, however no clear guidelines exist.

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Guidelines

National society guidelines

Title	Source	Date and reference/weblink
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Management of Patients With Acute Lower Gastrointestinal Bleeding	American College of Gastroenerology	2016 https://journals.lww.com/ajg/Fulltext/2016/04000/ACG_Clinical_Guideline__Management_of_Patients.14.aspx
The Role of Endoscopy in the Management of Suspected Small Bowel Bleeding	American Society of Gastrointestinal Endoscopy	2016 https://www.asge.org/docs/default-source/education/practice_guidelines/suspected_small_bowel_bleeding.pdf?sfvrsn=15c5951_6
The Role of Endoscopy in the Management of Variceal Hemorrhage	American Society of Gastrointestinal Endoscopy	2014 https://www.sciencedirect.com/science/article/pii/S0016510713021391?via%3Dihub
The Role of Endoscopy in the Management of Patient With Peptic Ulcer Disease	American Society of Gastrointestinal Endoscopy	2010 Gastrointest Endosc 2010;71(4):663–8
Portal Hypertensive Bleeding in Cirrhosis	American Association for the Study of Liver Diseases	2016 https://www.aasld.org/sites/default/files/2019-06/Garcia-Tsao_et_al-2017-Hepatology.pdf

International society guidelines

Title	Source	Date and weblink
Diagnosis and Management of Nonvariceal Upper Gastrointestinal Hemorrhage: ESGE Guidelines	European Society of Gastrointestinal Endoscopy (ESGE)	2015 https://www.esge.com/assets/downloads/pdfs/guidelines/2015_s_0034_1393172.pdf

Evidence

Type of evidence	Title and comment	Year and reference
RCT	*Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial* More definite diagnoses were achieved with urgent colonoscopy	2005 Green BT, et al. Am J Gastroenterol 2005;100:2395–402
RCT	*Randomized trial of urgent vs elective colonoscopy in patients hospitalized with lower GI bleeding* There was no difference in clinical outcomes or cost between colonoscopy performed at <12 hours compared to 36–60 hours	2010 Laine L, Shah A. Am J Gastroenterol 2010;105:2636–41
Case–control	*Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage* Urgent colonoscopy with endoscopic therapy reduced rebleeding and need for surgery	2000 Jensen DM, et al. N Engl J Med 2000;342:78–82

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 34

Acute Abdomen and Abdominal Sepsis

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OVERALL BOTTOM LINE

- An acute abdomen denotes rapid onset of severe abdominal symptoms which may require urgent surgical intervention.
- An orderly, expeditious and thorough investigation must proceed with history, physical examination, and laboratory and imaging studies.
- Abdominal sepsis is the response of the body's systemic inflammatory system to peritonitis, and is associated with a significant morbidity and mortality.
- Prompt recognition, resuscitation, antibiotics, and source control are critical factors affecting the prognosis of patients with abdominal sepsis.

Background

Definition of disease

- An acute abdomen is defined as the abdominal signs and symptoms of pain and tenderness that present with such sudden severity that emergency surgery is being considered.
- Abdominal sepsis is defined as an intra-abdominal infectious source that results in severe sepsis or septic shock.

Disease classification

Acute abdomen and abdominal sepsis can be further classified into primary, secondary, or tertiary peritonitis.

Incidence/prevalence

- Hospitalization for severe sepsis: there is a national incidence rate of three cases per 1000 population in the USA.
- About 8.6% of severe sepsis admissions are secondary to the abdominal source.
- About 36% of ICU admissions with severe sepsis have the abdomen as the attributable site.

Etiology

- Intra-abdominal infections (such as appendicitis, cholecystitis).
- Perforated abdominal viscous.
- Obstruction (volvulus, incarcerated hernia).
- Ischemia (ischemic colitis, mesenteric thrombosis).
- Hemorrhage (solid organ trauma, hemorrhagic pancreatitis).

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Pathology/pathogenesis

- The acute abdomen typically presents initially with poorly localized visceral pain, secondary to hollow viscous distension, infection, obstruction, or ischemia, which then localizes more anatomically as the pathology progresses.
- Abdominal sepsis results when there is an introduction of microorganisms into the peritoneal cavity. The result is an inflammatory response by the peritoneum with increased blood flow and permeability, and a subsequent sepsis syndrome.

Predictive/risk factors for abdominal sepsis

- Chronic diseases: AIDS, COPD, malignancy.
- Use of immunosuppressive agents.
- Advanced age.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Prompt recognition of an abdominal pathology and source control prior to systemic spread is the only intervention which has been shown to prevent abdominal sepsis.

Secondary prevention

- Initial source control.
- Open abdomen management (laparostomy) or on-demand expeditious re-laparotomy until source control is achieved.
- Systemic antibiotics.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Intensity, severity, and timing of abdominal pain complaints will aid with the differential diagnosis.
- The character of the pain and its location are also important to assist localization of the intra-abdominal disease process.
- Patients with an acute abdomen will typically present with peritonitis; on exam they may lie very still and have diffuse abdominal tenderness with percussion and light palpation. Additionally, a rigid abdomen represents diffuse peritonitis and urgent intervention is necessary.
- When patients are hemodynamically stable, CT scan is the optimal imaging modality for most intra-abdominal conditions.
- Laboratory testing should include blood count, electrolytes, and metabolic panel. Lactate may be useful when there is a question of bowel ischemia or infarction.

Typical presentation

- Patients typically present with abdominal pain, nausea, and changes in bowel habits.
- There is usually an accompanying systemic inflammatory response seen with fever, tachycardia, tachypnea, and hypoxia.

Clinical diagnosis

History

- The principal feature in the history-taking will be abdominal pain. Open-ended questions, which allow the patient to elaborate on the timing, character, location, duration, and radiation, are crucial to reaching a diagnosis. Associated symptoms will also aid in the diagnosis and in determining what the next step should be in the management.
- Inquiries into past medical and surgical history also help to increase or decrease the likelihood of certain conditions and are crucial to the history. In women, it is important to investigate the gynecologic history as these conditions can very commonly result in acute abdominal pain.
- A thorough history of medications is extremely relevant given that they can both create an acute abdomen as well as disguise one.

Physical examination

- The physical exam should begin with simple observation, as most patients with an acute abdomen or abdominal sepsis are uncomfortable and in distress. Important findings to look for include involuntary guarding and diffuse tenderness – especially with percussion/palpation.
- Signs of hypoperfusion, such as altered mental status, oliguria, or hypotension, signify a transition from sepsis to severe sepsis or septic shock.

Laboratory diagnosis

List of diagnostic tests

- Complete blood cell count: whenever an acute abdomen is present.
- Basic metabolic profile: when history suggests vomiting or diarrhea.
- Coagulation profile: when severe sepsis is suspected.
- Lactate level: when ischemia is suspected or an acute abdomen is present.

List of imaging techniques

- CT scan of the abdomen: when the abdomen is suspected as the source of sepsis.
- Upright abdominal X-ray: when perforated viscous is suspected.
- Ultrasound of abdomen.

Potential pitfalls/common errors made regarding diagnosis of disease

- Delay in diagnosis of intra-abdominal infection and abdominal sepsis.
- Delay in starting antibiotics.
- Delay in source control.

Treatment

Treatment rationale

- Whatever the source of abdominal sepsis is (e.g. abscess, infarcted bowel), it must be drained or removed in order for appropriate treatment to ensue.
- Hemodynamic support with fluid resuscitation and prompt IV antibiotics initiation per sepsis protocol.
- A re-laparotomy strategy may be pursued when source control is not obtainable on initial operation. The use of an open abdomen to implement re-laparotomies may play a pivotal role in the management of abdominal sepsis.

When to hospitalize

- Patients who present with an acute abdomen or abdominal sepsis will require hospitalization.

Managing the hospitalized patient

- Initial operation: the timing and adequacy of source control are the key factors in the management of abdominal sepsis.
- Aggressive critical care management.

Table of treatment

Treatment	Comments
Conservative	Percutaneous drainage of abdominal abscesses is safe for most appendiceal and diverticular abscesses with no evidence of diffuse peritonitis
Medical	Broad spectrum IV antibiotics should be initiated with the presentation of abdominal sepsis, narrowed according to sensitivity once cultures permit Early vasopressor agents (norepinephrine is first line agent) Inotropic agents (epinephrine) when indicated by myocardial dysfunction Corticosteroids may be initiated in refractory septic shock
Surgical	Laparotomy or laparoscopy with individual intervention determined by underlying pathology (e.g. appendectomy, bowel resection, gastric repair) Open abdomen with re-laparotomy when initial source control is not possible
Radiologic	Hemodynamically stable patients: CT abdomen and pelvis Unstable patients: upright abdominal X-ray or ultrasound

Prevention/management of complications

- Persistent intra-abdominal hypertension resulting in abdominal compartment syndrome can be seen with massive fluid resuscitation.
  - Use of open abdomen at the index operation with a delay of fascial closure can minimize this risk.

CLINICAL PEARLS

- Prompt recognition of the source of sepsis as intra-abdominal with rapid intervention and source control are key to management of abdominal sepsis.
- Rapid initiation of broad spectrum IV antibiotics with aggressive critical care management play a large role in the outcome of these patients.

Special populations

Pregnancy

The treatment of the acute abdomen and subsequent abdominal sepsis in pregnancy is the same as in the non-pregnant patient; the greatest roadblock to treatment in this patient population is a delay in diagnosis.

Children

The acute abdomen and abdominal sepsis are managed with similar strategies as seen with adults. The challenge to management with this population is that given the pediatric patient's decreased ability to provide adequate and thorough histories there can be a delay in reaching the correct diagnosis.

Elderly

The geriatric population may also present with diagnostic dilemmas. The increased incidence of dementia and other underlying comorbidities may result in a delay in diagnosis. A delay in diagnosis leads to a poorer prognosis.

Others

Immunosuppressed patients may present with minimal to no abdominal pain, and with an inability to mount a full inflammatory response, thus systemic signs of sepsis and laboratory tests may not show classic abnormalities. This group of patients may suffer from a delay in diagnosis, however the general treatment remains the same.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Prognosis is largely dependent on early diagnosis and source control.
- Aggressive resuscitation, early IV antibiotic administration, and hemodynamic support are crucial in improving prognosis.
- Critical care management should be started early when appropriate.

Natural history of untreated disease

- In the event of untreated abdominal sepsis, overwhelming systemic collapse ultimately ensues, leading to near certain mortality.

Prognosis for treated patients

- Many survivors of sepsis suffer from long-term impairments including renal failure and cognitive changes.

Reading list

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Guidelines

International society guidelines

Title	Source and comment	Date and weblink
WSES Guidelines for Management of Intra-Abdominal Infections	World Society of Emergency Surgery (WSES) Evidence based recommendations for the management of intra-abdominal infections	2013 http://wjes.biomedcentral.com/articles/10.1186/1749-7922-8-3
SCCM Guidelines for the Management of Severe Sepsis and Septic Shock	Society of Critical Care Medicine (SCCM) Consensus of expert panel for the management of sepsis	2012 http://www.sccm.org/Documents/SSC-Guidelines.pdf

Additional material for this chapter can be found online at:
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This includes multiple choice questions.

with website

CHAPTER 35

Abdominal Compartment Syndrome

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OVERALL BOTTOM LINE

- A high index of suspicion is necessary to identify at-risk patients and prevent abdominal compartment syndrome (ACS).
- Diagnosis requires sustained elevated intra-abdominal pressure (IAP) greater than 20 mmHg and new end-organ dysfunction.
- Presumptive decompression should be considered at initial laparotomy in patients with multiple risk factors for intra-abdominal hypertension (IAH).
- Decompressive laparotomy with open abdomen management is the standard of care.

Background

Definition of disease

- ACS is defined as a sustained IAP >20 mmHg that is associated with a new organ dysfunction or failure.
- Normal IAP in critically ill patients is 5–7 mmHg and IAH is defined by sustained or repeated elevation of IAP >12 mmHg.

Disease classification

- Primary ACS is associated with injury/disease in the abdomino-pelvic region.
- Secondary ACS refers to conditions that do not originate from the abdomino-pelvic region, such as large volume resuscitation.

Etiology

- Primary ACS can result from free ruptured abdominal aortic aneurysms, abdominal trauma, retroperitoneal hemorrhage from pelvic trauma, acute gastric dilation, severe pancreatitis, abdominal packing, repair of gastroschisis or omphalocele, and reduction of large hernias as well as other causes.
- Secondary ACS can result from mangled extremities, burns, systemic inflammatory response syndrome (SIRS), or septic shock.

Pathology/pathogenesis

- The pathophysiology of ACS is best understood by examining the different systems affected by the ACS.
- Cardiovascular dysfunction is revealed as a decrease in cardiac output (CO) as IAP increases. The IAH results in direct compression of the IVC/portal flow causing a decrease in venous return. Intrathoracic

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displacement of the diaphragm causes an increased thoracic pressure. This increased thoracic cavity pressure results in cardiac compression and decreased cardiac compliance. Coupled with increased systemic afterload seen with IAH, the result is failure of adequate CO.

- Pulmonary system dysfunction is caused by increases in IAP that displace the diaphragm leading to reduction in total lung capacity, functional residual capacity, and residual volume. All of these reductions produce ventilation–perfusion abnormalities that ultimately result in hypoxia and hypercarbia.
- Renal derangements are expressed clinically as oliguria, which then progresses to anuria and eventually pre-renal azotemia that does not respond to volume. The failure of volume administration to correct an oliguric state is likely secondary to compression of renal outflow. There is a reduction in renal blood flow (caused by decreased CO and direct compression) with increased renal vascular resistance and subsequent reduced glomerular filtration.
- Intestinal dysfunction results from decreases in mesenteric arterial, hepatic arterial, intestinal mucosal, and portal venous blood flow. These impaired flow states seen with increasing IAH all lead to impaired intestinal perfusion which can result in intestinal ischemia and, if untreated, subsequent necrosis.

Predictive/risk factors

- Hemorrhage.
- Primary closure of abdominal wall.
- Reduction of diaphragmatic hernias.
- Damage control laparotomy.
- Massive fluid resuscitation.
- Poly trauma/burn injuries.
- Prone positioning.
- Intra-abdominal or retroperitoneal tumors.
- Acute pancreatitis.
- Gastroparesis/gastric distention/ileus.
- Intra-abdominal sepsis/abscess.
- Acute ascitic cirrhosis/liver dysfunction.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Prophylactic open abdomen should be performed in damage control trauma laparotomy.
- Appropriate sedation and analgesia should be given to critically ill patients.
- Enteral decompression should be performed when the stomach and colon are dilated.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Identification of at-risk patients: major abdominal/thoracic operations requiring large amounts of IV fluid resuscitation; trauma or burn patients who fail to respond to ongoing fluid losses; patients requiring massive transfusion protocols.
- Do *not* rely on physical exam or measurement of abdominal girth as it is extremely non-specific and does not reliably correlate with IAH/ACS.
- IAP should be measured via the urinary bladder in identified high risk patients.
- There should be accurate monitoring of urinary output, peak inspiratory airway pressures, and CO in patients in whom IAP is being measured.

Typical presentation

- The typical presentation of ACS is a critically ill patient in the ICU who has undergone massive resuscitation for any reason (trauma, surgery, burns, pancreatitis, etc.) and develops increasing abdominal distension, edema, and worsening ventilatory status.
- In this setting the beginnings of multiorgan failures become evident with oliguria/anuria, hypotension, increased peak airway pressures, and eventual cardiac arrest.

Clinical diagnosis

History

- History of recent abdomino-pelvic trauma.
- Extended laparotomy time.
- Large volume resuscitation.

Physical examination

- Physical exam is unreliable in the diagnosis of ACS.

Useful clinical decision rules and calculators

- https://www.wsacs.org/images/algorithms/IAH_ACS_management_2014.pdf.
- https://www.wsacs.org/images/algorithms/IAH_ACS_medical_management_2014.pdf.

Disease severity classification: grading system for intra-abdominal hypertension

Grade	Intra-abdominal pressure (mmHg)
I	12–15
II	16–20
III	21–25
IV	>25

Based on information from the World Society of the Abdominal Compartment Syndrome.

Laboratory diagnosis

List of diagnostic tests

- Measurement of bladder pressure provides an indirect estimate of intraabdominal pressure.
- Observance of increasing peak airway pressures.
- Increasing BUN/creatinine levels (very late sign, often too late at this point).

List of imaging techniques

- CT abdomen is the most widely available and informative method for evaluating causes of ACS (e.g. abscess, ischemic bowel, retroperitoneal hematoma, ileus, perforated viscus with free air).

Potential pitfalls/common errors made regarding diagnosis of disease

- Dependence on physical exam for diagnosis.
- Low index of suspicion.

Treatment

Treatment rationale

The definitive treatment for ACS is a decompressive laparotomy.

Managing the hospitalized patient

- Decompressive laparotomy and management of open abdomen.
- Use of negative pressure wound dressing for open abdomen.
- Continual and gradual daily attempt at closure of abdomen.

Table of treatment

Treatment	Comments
Medical	Adequate sedation and analgesia in patients with IAH Brief paralysis with IAH
Surgical	Decompressive laparotomy
Complementary	Enteral decompression with either rectal or nasogastric decompression in patients with IAH and enteral dilation

Prevention/management of complications

- Inability to close abdomen primarily after decompressive laparotomy: can be managed with planned ventral hernia and subsequent hernia repair.
- Development of enteroatmospheric fistulae: can be managed with NPO status, parental nutrition, and attempt to control or stop fistulous output.

Reading list

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Cheatham ML, Safcsak K. Is the evolving management of intra-abdominal hypertension and abdominal compartment syndrome improving survival? Crit Care Med 2010;38:402.

Kirkpatrick AW, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 2013;39:1190–206.

Rogers WK, Garcia L. Intraabdominal hypertension, abdominal compartment syndrome, and the open abdomen. Chest 2018;153:238–50.

Guidelines

International society guidelines

Title	Source	Date and weblink
Intra-abdominal Hypertension and the Abdominal Compartment Syndrome: Updated Consensus Definitions and Clinical Practice Guidelines	World Society of the Abdominal Compartment Syndrome	2012 http://www.wsacs.org/images/2013%20Guidelines%20slide%20set.pdf

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 36

Acute Mesenteric Ischemia

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OVERALL BOTTOM LINE

- Acute mesenteric ischemia (AMI) is a life-threatening condition. Early recognition and treatment is critical for survival.
- The general prognosis is poor, especially for patients with arterial AMI, with acute mesenteric arterial embolism carrying the worst 5 year survival rate.
- After diagnosis, initial treatment with anticoagulation, fluid resuscitation, and revascularization is paramount.
- Advanced presentations of AMI may not be salvageable and palliation should be considered.

Background

Definition of disease

- AMI is defined as a sudden loss of blood flow to the small intestine.
- The loss of intestinal flow may be due to superior mesenteric artery or portal venous obstruction, although arterial etiologies predominate.

Disease classification

There are four classifications within AMI:

- Acute mesenteric arterial embolism (AMAE).
- Acute mesenteric arterial thrombosis (AMAT).
- Non-occlusive mesenteric ischemia (NOMI).
- Mesenteric venous thrombosis (MVT).

Incidence/prevalence

- AMI is seen in around one out of every 1000 hospital admissions, and has an annual incidence of between 0.1% and 0.2% per patient year.
- Because it primarily affects older patients, the incidence of AMI is expected to rise with the aging population.

Etiology

- AMAE is most commonly caused by an embolus in a patient with atrial fibrillation, but also can be iatrogenic or from arterial–arterial embolization.
- AMAT is most often the result of progressive atherosclerosis. Less common causes include spontaneous superior mesenteric artery (SMA) dissection, aortic dissection, aneurysm, and arterial vasculitis.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- NOMI can be caused by secondary hypotension from septic shock, heart failure, and the use of vasoactive medications.
- MVT has several etiologies, including abdominal tumors, gastrointestinal infection, and portal hypertension.

Pathology/pathogenesis

- AMAE: Emboli, most frequently of cardiac origin or from a ruptured thrombus, lodge in mesenteric arteries (most commonly in the SMA) leading to acute ischemia.
- AMAT: Thrombosis of the mesenteric arteries due to chronic atherosclerosis leads to ischemia. Arterial aneurysms, dissections, and vasculitis can all also lead to acute thrombosis.
- NOMI: Secondary vasoconstriction caused by hypovolemia, shock, and vasoactive drugs leads to decreased mesenteric perfusion.
- MVT: Virchow's triad – namely hypercoagulability, venous stasis, and endothelial damage – can result in thrombosis.

Predictive/risk factors

Risk factor	Odds ratio
Atrial fibrillation	1.2
Diabetes	2.4
Coagulopathies	8.1

Prevention

BOTTOM LINE/CLINICAL PEARLS

- No interventions have been demonstrated to prevent the development of the disease beyond the management of risk factors (such as anticoagulation for patients with atrial fibrillation).

Screening

- Lactic acid elevation is useful for diagnosing and trending possible ischemic bowel.

Primary prevention

- Anticoagulation of patients with atrial fibrillation.
- Antiplatelet agents, antihypertensive medications, and cholesterol management, particularly statins in patients with known atherosclerosis and atherosclerosis risk factors.
- Hydration of patients at risk for MVT.

Secondary prevention

- In patients with new onset atrial fibrillation who have been treated for embolism, continued anticoagulation is needed.
- Anticoagulation will help prevent progression and recurrence of MVT.
- Intra-arterial papaverine may relieve and prevent recurrence of NOMI.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- In the right presentation, physicians should have an increased suspicion of AMI. A history of atrial fibrillation, past embolic events, myocardial infarction, atherosclerotic disease like CAD/PAD, a long smoking history (AMAT), and/or any coagulopathies are suggestive.
- Physical exam findings may or may not be reflective of peritoneal inflammation, but generally gastrointestinal signs like abdominal pain, nausea, vomiting, and diarrhea are neither specific nor sensitive.
- Abdominal pain that is out of proportion to the physical exam is a hallmark sign of AMI.
- The gold standard for confirmation is CT angiography, which has a >90% sensitivity and specificity for detection of AMI.

Differential diagnosis

Differential diagnosis	Features
Gastroenteritis	Vomiting Diarrhea
Ischemic colitis	Different clinical setting Pain LLQ History of aortic manipulation
Ruptured abdominal aortic aneurysm	Sudden hypotension Pulsating abdominal mass + FAST exam History of aneurysm
Bowel obstruction	Prior surgery Distention Vomiting
Appendicitis	RLQ pain
Cholecystitis	RUQ pain

Typical presentation

- It is classically taught that patients with AMI present with abdominal pain that is out of proportion to the physical exam (due to the lack of initial peritoneal signs).
- The onset of pain varies with the etiology of the AMI; typically AMAE and AMAT present in an acute setting, NOMI is more of a slowly progressive process, while MVT can fall in either category.
- Patients also commonly present with nausea, vomiting, diarrhea, and subsequent constipation. Hematochezia is another potential presentation of AMI. AMI tends to occur in older patients (age >60 years) with the exception of MVT which is seen in patients in their forties.

Clinical diagnosis

History

- Because of the non-specific physical exam findings associated with AMI, clinicians should take a detailed history.
- A past medical history of previous embolic events or recent myocardial infarction would be concerning for AMAE, while a long history of atherosclerotic disease is more indicative of AMAT.

- Infection/sepsis can predispose to NOMI and less commonly AMAT.
- A patient's past surgical history can provide additional insight, specifically recent abdominal surgeries in the case of MVT and vascular bypass surgeries in the setting of AMAT.
- The use of oral contraceptives, liver disease, malignancy, and congenital hypercoagulable states should be explored when MVT is suspected.

Physical examination

- A focused abdominal exam should be done, with particular attention to auscultation and palpation. Depending on the progression of the disease, peritoneal signs such as abdominal distension, rebound tenderness, and guarding may be appreciated. In addition, bowel sounds might be absent.
- Other physical exam findings are dependent on the etiology of the AMI and the corresponding risk factors. Irregularly irregular heart sounds may be appreciated on cardiac auscultation in the case of AMAE.

Laboratory diagnosis

List of diagnostic tests

The following laboratory tests should be drawn for all patients:

- D-dimer: D-dimer is elevated early in the course of AMI, although the magnitude of elevation does not correlate with severity.
- CBC: Leukocytosis is seen in around half of patients with AMI.
- ABG: Metabolic acidosis is a late laboratory finding in patients with AMI, while metabolic alkalosis can be an early finding if the patient has vomited excessively. An elevated lactate is common.
- PT/PPT/INR: These tests are used to evaluate patients for hypercoagulable states.

List of imaging techniques

- CT angiography: This is the gold standard and preferred imaging technique with high sensitivity and specificity.
- Ultrasound: US is less sensitive than CT, but can be done if MVT is the suspected etiology or CT is contraindicated. This modality is made more difficult by the deep location of the mesenteric arteries, compounded by the abdominal distention that may accompany AMI.
- MRI: Because of the time taken to perform an MRI, it is not considered first line for an emergent condition like AMI.
- Arteriogram: This used to be a first line diagnostic test, and may still be considered if initial CT angiography is equivocal. A benefit of this technique is that it may also allow therapeutic intervention.

Potential pitfalls/common errors made regarding diagnosis of disease

- The most common error is mistaking AMI for gastroenteritis.

Treatment

Treatment rationale

- Initial management regardless of etiology involves anticoagulation and antibiotics, in addition to hemodynamic stabilization and pain management.
- Next, patients should undergo appropriate imaging to determine the surgical approach for treatment.
- Exploratory laparotomy is required in all cases of AMAE and AMAT, and should be performed selectively in NOMI and MVT.
- Necrotic bowel should be resected (Figure 36.1). Delayed bowel reconstruction is preferable after a second-look exploration.
- AMAE: Embolectomy is the first line. Infusion of thrombolytic is second line but only if the patient has not been symptomatic for a sustained period of time (<8 hours).

- AMAT: Mesenteric bypass or endarterectomy with patch angioplasty. Retrograde stenting may be possible in select cases.
- NOMI: Treat underlying cause.
- MVT: Continuous anticoagulation.
- A second-look operation should be performed to minimize removal of viable gut.

Table of treatment

Treatment	Comments
Medical AMAE and AMAT: heparin 80 U/kg bolus followed by 18 U/kg/h infusion AMAE: thrombolytic infusion can be considered if patient has been symptomatic for <8 hours NOMI: vasodilators can be used. Papaverine infusion 60 mg/h selectively in the superior mesenteric artery MVT: heparin 80 U/kg bolus followed by 18 U/kg/h infusion	Heparin monitoring should be performed by trending aPTT Papaverine should not be administered in the same setting as heparin or its derivatives
Surgical AMAE: laparotomy followed by embolectomy. Bypass if embolectomy fails AMAT: laparotomy followed by bypass. Endarterectomy if bypass is not an option AMAE, AMAT: endovascular treatments, including thrombectomy, thrombolysis, and/or angioplasty and stenting can be considered alongside surgical therapy. Second-look operation should be done between 24 and 48 hours after initial procedure NOMI and MVT: laparotomy in very select cases MVT: can consider TIPS with directed thrombectomy and thrombolysis in very select cases that are refractory to anticoagulation	

Prevention/management of complications

- Heparin can cause bleeding and heparin-induced thrombocytopenia; in the latter case, heparin should be discontinued and substituted for an alternative anticoagulant.
- As a side effect of resection, patients may suffer from short gut syndrome, for which treatment is individualized but ranges from total parenteral nutrition to taking anti-diarrheal medication.
- Another potential complication is myocardial infarction, especially in patients with AMAT. This can be avoided by close hemodynamic monitoring during the perioperative period.
- AMI has a poor prognosis, and, therefore, a prolonged hospital course and possible death are not uncommon.

CLINICAL PEARLS

- Patients should be given anticoagulation and antibiotics as soon as possible.
- Imaging findings will help determine medical/surgical approaches.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Prognosis is etiology dependent but in general very poor.
- Overall 5-year survival post-AMI is under 50%.

Natural history of untreated disease

- If AMI is not treated, the ischemia will progress to infarction, then peritonitis, and eventually death.

Prognosis for treated patients

- The prognosis for treated patients is poor, with the overall 5-year survival rate under 50%.
- The etiology of AMI does play a role, as patients with ischemia of arterial origin have a significantly higher mortality rate than patients with ischemia of venous origin.
- To subdivide even further, arterial embolic disease patients have a higher mortality rate than arterial thrombotic disease patients due to the associated greater degree of bowel infarction.

Follow-up tests and monitoring

- Patients should be scheduled for a mesenteric duplex ultrasound at 1 month post operation, followed by every 3 months for the first year.

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Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med 2004;164(10):1054–62.

Guidelines

National society guidelines

Title	Source	Date and weblink
ACC/AHA 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease	A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines	2005 https://www.ncbi.nlm.nih.gov/pubmed/16549646

International society guidelines

Title	Source	Date and weblink
ESTES Guidelines: Acute Mesenteric Ischaemia	European Society for Trauma and Emergency Surgery	2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4830881/

Evidence

Type of evidence	Title and comment	Date and weblink
Retrospective cohort study	*Comparison of Open and Endovascular Treatment of Acute Mesenteric Ischemia.* This study showed that endovascular therapy was a viable alternative to open surgery	2014 http://www.sciencedirect.com/science/article/pii/S0741521413012792

Image

Figure 36.1 Necrotic bowel. (See website for color version.)

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions and Figure 36.1 is available in color..

with website

CHAPTER 37

Surgical Trauma

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OVERALL BOTTOM LINE

- Trauma remains one of the leading causes of fatality in all age groups worldwide.
- Prevention is largely a matter of public service efforts to enhance societal education and counseling strategies and the implementation of environmental safety mechanisms.
- All trauma patients should be approached and triaged using the same method, with performance of primary and secondary surveys in conjunction with obtaining pertinent patient history.
- Definitive investigation and management is specific to the individual patient, but emphasis should be placed on rapid management of the most likely sources of morbidity and mortality.
- Prognosis is variable, but improved functional outcomes occur with appropriate rehabilitation methods and long-term multidisciplinary continuity of care.

Background

Definition of disease

- Trauma is injury due to an often sudden external force that affects one or many aspects of the body. Injury can be minor or it can be fatal.

Incidence/prevalence

- Trauma is the fifth leading cause of death in the USA and the leading cause of death in people aged 1–44 years.
- A fatal injury occurs nearly every 5 minutes.
- By 2020, it is estimated that one in 10 people worldwide will die as a result of trauma.

Economic impact

- In recent years, annual medical costs associated with injury and consequent loss of civilian work productivity in the USA has totaled over $500 billion.

Etiology

- Blunt injury comprises about 75% of all trauma; penetrating injury accounts for the majority of the remainder; with blast, thermal, caustic, electrical, and radiation injuries comprising a small portion.
- Approximately 70% of traumas are unintentional.
- Traumatic brain injury (TBI) is the most common ultimate cause of death in the USA with over 2 million TBIs occurring annually.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- Motor vehicle crashes are the leading mechanism of traumatic death.
- Firearm-related deaths are rising, and comprise the third leading cause of death in children between the ages of 10 and 19 years in the USA.
- Falls are responsible for the majority of all deaths in people older than 65, and are the leading cause of non-fatal injuries in all age groups.

Pathology/pathogenesis

- Trauma is a heterogeneous process with variable manifestations depending on mechanism and energy of injury, location of injury, and the patient's degree of physiologic plasticity.
- Broadly speaking, mortality following trauma follows a trimodal distribution:
  - 50% of people die immediately, 30% within the first few hours (a potentially salvageable period with appropriate interventions), and 20% die 1–3 weeks following the injury (often due to sepsis and multiorgan system failure).
- Advanced trauma and life support initiatives mainly target the second peak where specific early interventions can prevent morbidity or mortality

Predictive/risk factors

- Lower socioeconomic status is associated with a higher proportion of overall trauma as well as interpersonal and domestic violence.
- Men are nearly three times as likely as women to become victims of trauma and are more likely to engage in violence.
- People at extremes of age suffer proportionally higher fatality due to trauma.
- Elderly have the highest rates of suicide.
- Children are most likely to drown.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Unintentional trauma can be reduced with public education programs and environmental safety changes.
- The foundation of intentional trauma is complex and multifactorial and is therefore more difficult to prevent on a large scale.
- Myriad injury prevention and control organizations have been developed to reduce trauma in the USA and are the subject of ongoing investigation.

Screening

- Factors that predispose to trauma are more easily determined retroactively and are difficult to predict.
- Implementation of alcohol abuse screening programs has been shown to reduce recidivism. The American College of Surgeons Committee on Trauma has mandated brief intervention initiatives in trauma patients testing positive for alcohol.

Primary prevention

- As trauma mechanisms are distinct in different groups of people, preventive initiatives target different age groups and different sources of injury.
- In general, unintentional trauma is more easily preventable than intentional because of the multiple social, economic, and psychological factors involved in the latter.

- Use of automobile seat belts has been shown to reduce injuries and fatalities.
- Injury prevention counseling in families with children and among the elderly has been shown to reduce unintentional trauma.
- Gun safety initiatives in public service announcements and primary care settings may reduce firearm-related injuries.

Secondary prevention

- Secondary prevention follows the same basic strategy as primary prevention.
- Victims of trauma are often more prone to subsequent trauma than the general population. Targeted behavior modification and education may reduce the risk of recurrence.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Triage and evaluation of a trauma patient should always follow the same initial algorithm to ensure a thorough assessment.
- In conjunction with ascertaining injury-related context provided by on-scene witnesses or patient transporters, initial assessment with a primary survey should include evaluation of airway, breathing, circulation, disability, and exposure (i.e. 'ABCs' or 'ABCDE').
- If the patient is stable, the examiner should proceed to the secondary survey in conjunction with obtaining a patient history (AMPLE, see History section).
- A complete set of laboratory tests should be sent and the patient may undergo various imagings specific to the injury.

Typical presentation

- Presentation of the trauma patient is highly variable.
- Individual trauma centers often have guidelines that specify criteria for activating different levels of trauma management. Different types of trauma are specific to geographic regions (e.g. an urban location may encounter proportionally higher penetrating traumas).
- Generally speaking, a level 1 trauma center is the best equipped and receives patients with blunt and penetrating trauma in all age groups. It should have all the necessary resources to manage a critically ill patient including 24 hour surgical staffing, immediate access to imaging modalities and the operating room, and available surgical specialists (e.g. neurosurgery, orthopedic surgery).

Clinical diagnosis

History

- History in a trauma patient may sometimes be suboptimal due to the patient's mental status and a lack of bystanders familiar with the patient.
- A thorough trauma history should be specific and limited to information pertinent to the circumstance; it should be detailed enough to help guide differential diagnoses but not so drawn out to delay necessary evaluations or interventions.
- The examiner should first inquire about circumstances of the injury to set a context, often provided at time of presentation, as mechanism of injury can provide clues.
- AMPLE questions should be ascertained:
  - **A**llergies.
  - **M**edication.

- **P**ast medical history including tetanus status.
- **L**ast meal.
- **E**vents leading to injury.

Physical examination

- The examination should begin with rapid assessment of the most critical potential sources of early mortality, the patient's airway, breathing, and circulation ('ABCs'), while the patient's clothing is removed to provide complete exposure.
- Ask the patient to speak, visualizing the work of breathing, assessing jugular venous distension and tracheal position, and listening for breath sounds to quickly evaluate airway patency and respiratory compromise.
- Heart rate and blood pressure in conjunction with a pulse examination provide information on the circulatory system.
- Disability or the patient's neurologic status should also be assessed by speaking to the patient and assessing responsiveness, evaluating pupillary response, and monitoring extremity movement (patient history is useful, as abnormalities could signify stable baseline or traumatic brain injury with impending intracranial herniation).
- If ABCs are intact, a secondary survey should proceed with a thorough head-to-toe examination.
- This should include inspection and palpation and a neurologic assessment.
- It is crucial to log roll the patient to examine all areas (while maintaining cervical spine precautions if there is concern for a neck injury).
- Following initial treatment, a tertiary survey must be conducted including a thorough review of the patient's medical record and pertinent comorbidities and thorough repeat examination to search for missed injuries.

Useful clinical decision rules and calculators

- A patient with diminished neurologic function, equal to or less than a Glasgow Coma Scale (GCS) score of 8 should be considered for intubation for airway control.
- If a patient is intubated for respiratory distress, a CXR should be obtained as soon as possible to rule out a pneumothorax which could be exacerbated by intubation.
- Emergency department thoracotomy should be considered in a penetrating injury with signs of life (SOL) at the scene of injury and loss of SOL 5 minutes prior to ED arrival, or blunt injury in which SOL were lost on arrival to the ED.

Disease severity classification

- A multitude of trauma scoring systems have been developed over the past 30 years, but none have been universally accepted by all trauma authorities.
- While many provide useful information for prognostication and management, their main utility is in research and comparison of hospital outcomes.
- Scoring systems can generally be divided into anatomic and physiologic scores.
- The Injury Severity Score (ISS), calculated based on degree of injury to one of six body regions, has been shown to predict mortality, and is probably the most widely use anatomic method (www.mdcalc.com/injury-severity-score-iss).
- The Revised Trauma Score (RTS) is the most widely used physiologic measure. It incorporates GCS score, a 15 point assessment of neurologic function, as well as respiratory rate and blood pressure (www.mdcalc.com/revised-trauma-score). It has similarly been shown to correlate well with survival and is a useful adjunct in triage decision making.

Laboratory diagnosis

List of diagnostic tests

- Many laboratory tests are patient specific and may not be of initial use in an unstable patient needing urgent intervention.
- Typical initial tests include:
  - Complete blood count (CBC) to establish a baseline hemoglobin and platelet count.
  - Basic metabolic profile (BMP) to determine kidney function, electrolyte abnormalities, and blood glucose level.
  - Lactate level as an indicator of hypoperfusion.
- Alcohol and urine drug screen.
- Beta-human chorionic gonadotropin (β-HCG) to diagnose pregnancy in a woman of child-bearing age.
- Arterial blood gas (ABG) if concern exists for acid–base abnormality or pulmonary dysfunction.
- Prothrombin time (PT) or international normalized ratio (INR) in a patient taking warfarin.
- Blood type and cross in a patient likely to need blood product transfusions.
- Urinalysis or urine dipstick if possible genitourinary trauma occurred and if there is concern for rhabdomyolysis or infection.

List of imaging techniques

- Radiologic studies should similarly be guided by mechanism of injury and examination.
- If other diagnostic methods are present, time-intensive imaging studies should be avoided in unstable patients.
- Common initial tests include the following (list is not comprehensive):
  - Typically all patients undergo electrocardiogram.
  - Chest X-rays are often routine, except in patients with isolated extremity penetrating injury.
  - Pelvic X-rays are used to evaluate blunt injuries.
  - Focused assessment using sonography for trauma (FAST): indicated for hypotension, chest or abdominal trauma, impaired consciousness, and pulseless electrical activity (may be obviated by diagnostic peritoneal lavage in abdominal trauma).
  - CT head: penetrating trauma to the head, or blunt trauma to the head with high energy mechanism, altered mental status or focal neurologic defect, headaches, or presence of anticoagulation.
  - CT spine: spine tenderness or new motor or sensory neurologic defects.
  - MRI spine: new motor or sensory deficits or persistent pain without bone disruption.
  - CT abdomen: abdominal tenderness or stable patients with blunt trauma and positive FAST, presence of macroscopic or microscopic hematuria, and low rib fractures.
  - Angiography neck: blunt neck trauma with new neurologic defect, penetrating neck trauma, first rib fractures.
  - Angiography chest: acceleration/deceleration injuries.
  - Bronchoscopy/esophagography/esophagogram: penetrating neck injuries.
  - Retrograde urethrogram: concern for urethral injury.
  - Extremity film: extremity tenderness.
  - Doppler arterial exam and arterial to brachial indices: abnormal or differential in pulse exam.

Diagnostic algorithms

- As trauma is a rather broad field, algorithms have been developed for many different types of injuries (see Guidelines section).
- Following initial resuscitation and FAST exam, clinicians assess stability and decide on whether abdominal imaging or laparotomy is necessary.

Potential pitfalls/common errors made regarding diagnosis of disease

- Sole focus on one specific site of injury can lead to delay in or failure to recognize concurrent life-threatening injuries.
- Patients at extremes of age, trained athletes, pregnant patients, and those taking medications may have altered physiologic responses, which can confound degree of illness.
- A normal hemoglobin level in the setting of blood loss may not be accurate as whole blood is lost.
- In a hemodynamically unstable patient with obvious head trauma, the temptation to image the head should be avoided in search of other sources as the head is rarely a source of hypotension and is less likely to cause imminent death.
- Blast and firearm injuries may cause more extensive damage at the cellular level than can initially be recognized grossly.

Treatment

Treatment rationale

- Treatment should begin as soon as the patient presents and should occur in concert with evaluation.
- Initial steps include placement of two preferably large bore IVs (or central venous access) and initiation of oxygen by nasal cannula or facemask.
- In patients with blunt trauma, a cervical collar should be placed for cervical spine immobilization until the extent of injury is determined.
- As with triage and diagnosis, treatment should be individualized.
- Initial management is guided by ABCs, which will sequentially identify the earliest and most threatening potential sources of mortality.
- After airway and breathing have been deemed intact, focus should shift to causes of circulatory compromise, as hemorrhage is the predominant cause of preventable death.
- Other causes of hypotension including cardiogenic, obstructive, and neurogenic shock should be ruled out.
- Initiation of warmed isotonic IV fluids should begin on any patient with a systolic blood pressure <110 mmHg and a heart rate >100 beats/min with a rapid search to identify the origin of blood loss
- Due to cost and its potential deleterious effects, colloids should be avoided.
- Frequent reassessment of resuscitation should occur (with clinical assessment, urinary output, laboratory values) to avoid under- or over-resuscitation.
- Initiation of blood product transfusion should be based on clinical judgment.
- In general, if an adult patient does not respond or transiently responds to 2 L of fluids and has a mechanism of injury concerning for possible hemorrhage, initiation of blood products should begin with a 1:1:1 blood product ratio (PRBC : FFP : PLT) to avoid coagulopathy.
- Blood products should ideally be limited to maintain hemoglobin above 7 g/dl.

When to hospitalize

Transfer to a level 1 trauma facility should be considered in the following conditions:

- GCS ≤13, SBP <90, RR<10 or >20 in an adult.
- Two or more long bone fractures, mangled extremity or amputation, pelvic fracture, new paralysis.
- Penetrating injuries to the head, neck, torso, or proximal extremities.
- Falls in adults of ≥2 stories, or in children 2–3 times height.
- Significant blunt mechanism including automobile versus pedestrian or motorcycle accident >20 mph, ejection from vehicle, significant destruction to vehicle.

- Traumatic injury in a woman >20 weeks pregnant, burns in patients with traumatic mechanisms, and children and elderly with a significant mechanism and unreliable examination.

Managing the hospitalized patient

Two important concepts to consider in the critically ill patient include definitive airway control and damage control surgery.

Airway control

- Some indications for airway control include apnea, depressed consciousness (typically GCS ≤8), respiratory distress or respiratory compromise, airway obstruction or facial or neck injury with potential to compromise airway, combativeness or risk for deterioration with continued need for diagnostic or therapeutic interventions, cyanosis.
- Definitive airway control includes nasotracheal intubation, orotracheal intubation, and a surgical airway.
- Nasotracheal intubation is contraindicated in apnea, basal skull fracture, and some facial fractures.
- If accessible, endotracheal is the preferred route of intubation.
- If endotracheal intubation fails, a surgical airway must be placed.
- In adults, cricothyroidotomy is preferable to tracheostomy because it is easier, quicker, and causes less bleeding.
- Endotracheal intubation is temporary and may be converted to a tracheostomy as a definitive airway after 14 days if the patient is unable to be weaned from mechanical ventilation.
- If prolonged intubation is anticipated, consideration should be given to performing an early tracheostomy between days 3 and 7, which may reduce upper airway trauma, overall mortality, and length of hospital stay.

Damage control

- Damage control is a method of rapidly accomplishing the minimum necessary to stabilize the critically ill patient. It begins with resuscitation in the trauma bay, continues to the OR, followed by transport to the ICU for continued resuscitation. More definitive procedures (e.g. abdominal closure, bowel anastomosis) are performed after the patient is stable.
- Prevention of the lethal triad of hypothermia, acidosis, and coagulopathy is crucial.
- A damage control technique should be considered in patients requiring massive resuscitation (>10 units PRBC or >12 L fluids), continued acidosis (pH <7.2), hypothermia (<34°C), inaccessible vascular injuries or need to return to the OR for an additional reassessment, and patients with high peak airway pressure or difficulty closing the abdomen.
- An abdominal operation should identify and abolish hemorrhage and minimize intra-abdominal contamination.
- Temporary abdominal closure should be achieved with a vacuum-assisted device, which places tension on the abdominal fascia and does not harm visceral structures.
- Morbidity and mortality decreases proportionately with shorter duration of OR time until the abdomen is closed. As soon as the patient is hemodynamically stable and well resuscitated, abdominal closure should occur.
- Similar damage control concepts can be applied to management of thoracic, vascular, and orthopedic injuries.

Prevention/management of complications

- The third wave of trauma-related mortality is most often due to sepsis and multiorgan dysfunction syndrome (MODS).
- MODS is a complex process due to inflammatory or immune dysregulation with deleterious systemic effects.
- Prevention of MODS and sepsis begins in the initial stages of treatment.
- Management includes rapid identification of the cause, appropriate use of antibiotics when indicated, aggressive nutritional support, prevention of hypoxemia and hypotension, avoidance of nephrotoxic agents, use of lung protective ventilation strategies, limitation of blood product transfusions, and maintenance of euglycemia.

CLINICAL PEARLS

- Triage and treatment are intimately related; early management should focus on the most likely problems to result in death.
- In a patient with respiratory distress or at risk of losing an airway, a definitive airway should be placed.
- Resuscitation with warmed crystalloid fluids should be initiated in patients with signs of hypovolemia and should be concurrent with rapid identification and termination of the source of hemorrhage.
- In critically ill or injured patients, damage control management should be employed whereby the minimum necessary surgical intervention is performed to control bleeding and contamination to allow for prompt return to the ICU for continued resuscitation.

Special populations

Pregnancy

- The physiology of pregnancy alters response to injury.
- During pregnancy, cardiac output and heart rate increase (second trimester), intravascular volume expands but hematocrit decreases, the diaphragm rises 4 cm, the gravid uterus displaces viscera cephalad, and pelvic veins engorge increasing the risk of bleeding.
- Pregnant patients can lose up to one-third of blood volume without alteration in vital signs.
- The focus of management is to treat the mother, thereby also increasing the likelihood of fetal survival.
- Indications for CT scan in the pregnant patient are no different than a non-pregnant patient but protective lead should be applied over the fetus when possible.
- Indications for an emergency Cesarean delivery during exploratory laparotomy include maternal shock and pregnancy >34 weeks, abruption or disseminated intravascular coagulation putting mother at risk, risk of fetal distress exceeding immaturity, severe pelvic or lumbosacral injuries, and the uterus preventing exposure of necessary maternal structures.

Children

- Trauma is the leading cause of death in children, 90% are blunt injuries, and most fatalities are due to traumatic brain injury.
- Blood pressure in children is the poorest indicator of hemorrhage as it is well preserved for a longer time.
- Body surface area and head size are proportionally higher in children, predisposing to hypothermia and head and neck injury.
- After stabilization of the pediatric patient, transfer to a tertiary pediatric center for continued care as early as possible is warranted.

Elderly

- Falls are the most frequent cause of traumatic injury in the elderly population.
- Elderly patients have decreased ability to increase heart rate in response to hypotension, and use of polypharmacy may further blunt the response.
- Comorbidities (such as hypertension and dementia) may also make examination unreliable.
- Due to more frequent use of anticoagulants and antiplatelet medications, elderly patients are more prone to bleeding.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Prognosis varies widely based on severity and type of injuries as well as the individual's physiologic reserve and ability to recover.
- Many types of trauma can be permanently life altering, and early initiation of rehabilitation offers the greatest chance for functional recovery.

Follow-up tests and monitoring

- For many patients, a traumatic experience can profoundly alter the course of their life.
- A smooth transition between inpatient and outpatient care with implementation of necessary resources is crucial to patient recovery.
- Similar to the inpatient course, outpatient care should often be multidisciplinary with patient follow-up with the trauma surgeon and team, relevant specialists involved in the patient's care, and utilization of social and rehabilitation services.

Reading list

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Wilson WC, Grande CM, Hoyt DB. Trauma. Emergency Resuscitation, Perioperative Anesthesia, Surgical Management. London: Informa Healthcare, 2007.

Suggested websites

http://www.aast.org/default.aspx
http://www.east.org/
https://www.facs.org/quality-programs/trauma
http://www.iatsic.org
http://www.pediatrictraumasociety.org
https://www.wses.org.uk/guidelines

Evidence

Type of evidence	Title and comment	Date and weblink
RCT	*The CRASH-2 Trial: A Randomised Controlled Trial and Economic Evaluation of the Effects of Tranexamic Acid on Death, Vascular Occlusive Events and Transfusion* Requirement in Bleeding Trauma Patients Early administration of tranexamic acid in hemorrhaging trauma setting reduces mortality	2013 https://www.ncbi.nlm.nih.gov/pubmed/23477634
RCT	*Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma: The PROPPR Randomized Clinical Trial* 1:1:1 versus 1:1:2 blood product recuscitation reduces 24 deaths due to hemorrhage, but not overall mortality	2015 https://www.ncbi.nlm.nih.gov/pubmed/25647203
RCT	*Early Tracheostomy versus Prolonged Endotracheal Intubation in Severe Head Injury* In severe head injury early tracheostomy decreases mechanical ventilation time after development of pneumonia	2004 http://journals.lww.com/jtrauma/Abstract/2004/08000/Early_Tracheostomy_versus_Prolonged_Endotracheal.8.aspx
RCT	*Immediate Versus Delayed Fluid Resuscitation for Hypotensive Patients with Penetrating Torso Injuries* Delay of aggressive preoperative fluid resuscitation improves outcome	1994 http://www.nejm.org/doi/pdf/10.1056/NEJM199410273311701

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 38

Burns

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OVERALL BOTTOM LINE

- Burns are an important source of morbidity and mortality in the USA and worldwide.
- Burn patients should initially be assessed similarly to any other trauma patient as airway, breathing, and circulation are the greatest immediate threat to life.
- In severe burns, transfer to a burn center after initial resuscitation and stabilization is prudent as high volume centers will offer the greatest chance for survival.
- Adequate resuscitation and early wound closure are key to management.

Background

Definition of disease

- Burns are a heterogeneous disease characterized by tissue injury due to cellular damage from a transfer of energy with local and systemic consequences.

Incidence/prevalence

- The incidence of burn injuries has declined over the past several decades but remains a leading cause of accidental death in the USA and worldwide.
- About 1 million burn injuries occur annually in the USA and about 50 000 require hospitalization.
- Burn-related mortality is estimated to occur approximately every 3 hours in the USA and there are about 250 000 burn-related deaths per year worldwide.

Etiology

- The most common etiologies of burn are scald and flame injuries.
- The next most common in decreasing order of frequency are contact, electrical, and chemical burns.
- About 65% occur at home, 17% at work, 5% during recreation, 5% are self-inflicted, and the rest undisclosed.

Pathology/pathogenesis

- Typically, the severity of injury is determined by four factors: temperature of an object, amount of time in contact, location of injury, and specific heat of the object (or its ability to transfer energy). These factors contribute to burn depth and size, which are the ultimate determinants of severity of injury.
- Reversible protein degradation occurs above 40°C with permanent denaturation and coagulative necrosis starting at 45°C.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- The area of injury can be divided into three zones:
  - Coagulation (non-viable).
  - Stasis (salvageable).
  - Hyperemia (inflamed but viable).
- The early goal is to prevent progression of the zone of stasis and death of this tissue.

Systemic inflammatory response syndrome

- When a burn injures 20–30% of the total body surface area (TBSA), systemic manifestations occur. Release of inflammatory mediators results in macro- and microcirculatory dysfunction and multiorgan damage. Large fluid shifts occur from 'third spacing' of intravascular fluid and protein from capillary leakage and increased insensible fluid loss from open wounds and enhanced metabolic activity.
- In severe cases, burn shock occurs, which shares components of depressed myocardial function in combination with decreased intravascular volume.
- Fluid resuscitation is a necessity but over-resuscitation can exacerbate formation of edema and cardiogenic dysfunction.
- Within 48 hours, production and release of catecholamines, glucocorticoids, glucagon, and dopamine results in a hypermetabolic/catabolic state. Glycogenolysis and insulin resistance cause hyperglycemia, and increased lipolysis and proteinolysis provide further substrate for gluconeogenesis.
- In severe burns, protein loss can occur at a rate of up to 25 g/m^2 of burned tissue per day and is associated with impaired wound healing and immunity.
- Initial resting energy expenditure at time of admission is 140% of normal and can remain elevated at 110% 2–3 years later.
- Oliguria and kidney injury may develop without adequate resuscitation.
- Hepatic dysfunction occurs, and mucosal atrophy occurs in the gut.
- Depression of the reticuloendothelial system leads to decreased quantity and impaired functioning of immunologic cells.
- Most of these pathophysiologic mechanisms have been shown to correlate with severity of injury, and can improve with wound excision and closure.

Evolution of injury

- Without early and aggressive care by experienced providers, multiorgan failure and death can rapidly develop.
- Whereas partial thickness burns heal spontaneously from epidermal remnants and rarely scar, full thickness burns heal slowly from the wound edges.
- This slow process in combination with impaired immunity, weakened nutrition, and necrotic tissue substrate provide a viable environment for infection to develop, which is the leading cause of death in burns.
- As wounds heal, they contract and form hypertrophic scars, leaving functional and aesthetic deformities.

Predictive/risk factors for fire death

Risk factor	Relative risk
Age >85 years	4.6
Age <5 years	1.4
African-American	6.9
American-Indian	5.3

Other notable risk factors include mental or physical illness, use of sedative or illicit drugs, and military personnel.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- All burn injuries are technically preventable.
- The primary interventions that have reduced the incidence of burns over the past several decades include advancements in engineering, legal measures that have mandated safety regulations, and public education.

Primary prevention

- Multiple public health measures have contributed to a reduced incidence of burn injuries in the past two decades.
- The advent of and improvement in fire alarms have led to improved fire detection and the use of fire friendly materials, and sprinkler systems limit spread of fire after it develops.
- Safety mechanisms on electric devices, cooking appliances, and mechanical objects in addition to emergency exit routes at home and workplaces reduce the frequency and severity of injuries.
- Increased public awareness with educational programs in conjunction with improved fire professional proficiency have led to reduced incidence and more rapid triage and management of burn traumas.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Initial assessment of a burn patient should include evaluations of airway, breathing, and circulation followed by secondary survey in conjunction with history.
- An adequate history will reveal the age and comorbidities of the patient and may provide information on the mechanism and timing of the burn.
- Following a complete secondary exam, careful evaluation of wounds should be undertaken to quantify TBSI and assess location and depth of injuries.
- While diagnosis is primarily clinical, routine admission laboratory testing including CBC, BMP, lactate, carboxyhemoglobin, ARB, and CXR are performed for additional information.

Differential diagnosis

Differential diagnosis	Features
Frostbite	Tissue injury more likely to be symmetric and in sensitive areas including digits, nose, and ears
Exfoliative disorders (toxic epidermal necrolysis, Steven–Johnson syndrome, *Staphylococcus* scalded skin syndrome)	Appears as second degree burns and are often diffuse, affecting mucous membranes as well and accompany history of medication use or recent infection

Typical presentation

- Burns can occur in people of all ages and oftentimes patients or their families are a reliable source for mechanism of injury. In unaccompanied young children or in those with cognitive impairments, one should search for other clues.
- In fire and smoke-related incidents patients may present covered in soot with associated clothing damage.

- More common scald, flame, and contact injuries will present with erythema, blistering, severe pain and tenderness, or anesthesia at the site of injury depending on the severity.
- Electrical or chemical burns are more likely to be associated with specific recreational or occupational histories and but may otherwise have a similar physical presentation.

Clinical diagnosis

History

- Several important features of a history are useful in triaging a burn patient. The AMPLE (allergies, medications, past medical history, last meal, events) history is applicable to all trauma patients.
- The source of the burn (e.g. scald, electrical, chemical) is important for assessment and management of the injury.
- One should ascertain whether the patient was entrapped in a closed space, how much time has passed since the injury occurred, and whether there was loss of consciousness.
- Tetanus status should be ascertained.

Physical examination

- Evaluation of airway, breathing, and circulation, disability, and exposure are paramount in primary examination.
- Dyspnea or stridor, coughing up sputum, and singed hairs should raise suspicion for airway injury.
- Circumferential chest or extremity burns can impair breathing or circulation, respectively.
- One should maintain a relatively low threshold for intubation as rapid progression of airway edema can progress to a surgical emergency.
- Disability or altered consciousness may suggest other underlying conditions such as carbon monoxide or cyanide poisoning, hypoxia, or other conditions.
- Exposing the patient both removes a source of potential continued injury and permits assessment of extent of injury.
- In conjunction with a complete secondary examination, thorough assessment of burn size and depth is important to both guide initial management and to establish a baseline, as burns are dynamic and can convert to larger wounds over time depending on the recovery of the zone of stasis.
- Burn size can be estimated using the rule of nines or a Lund and Browder chart, and is critical for determining resuscitation, prognosis, disposition, nutritional support, and the need for potential surgical interventions.

Useful clinical decision rules and calculators

Rule of nines (Figure 38.1)

Calculation of fluid requirements

- After estimating the amount of burnt TBSA, the Parkland formula can be used to guide fluid resuscitation:
  - %TBSA × weight (kg) × 4 mL = total first 24 hour fluid requirement. Half should be given within the first 8 hours and the additional half over the subsequent 16 hours.
- While the Parkland formula is a useful tool, fluid resuscitation should ultimately be determined by clinical and laboratory findings. Generally, burns of <15% TBSA do not require resuscitation.
- In adults, the most important endpoint of resuscitation is urine output with a goal of 30 mL/h in adults or 0.5–1 mL/kg/h.
- Since significant capillary leakage occurs early following injury, resuscitation with crystalloids, not colloids, is the mainstay of resuscitation during the first 12–24 hours (primarily lactated Ringers' solution).
- Consideration should be given to colloids if fluid requirements far exceed those suggested by the Parkland formula.
- Nutrition requirement calculations are available at: http://www.surgicalcriticalcare.net/Resources/burn_nutrition.php.

Disease severity classification

- As shown in Table 38.1, burn degree can be determined by identifying various clinical findings. Historically, burns were described by several anatomic levels or 'degrees' (Figure 38.2). Today they are more commonly described by partial or full thickness, which focuses more on treatment distinction.

Laboratory diagnosis

List of diagnostic tests

- CBC, BMP, serum lactate, and ECG for all patients with burns >10% TBSA.
- ABG or VBG and carboxyhemoglobin level for enclosed space injury.
- Capnography and peak expiratory flow rates are useful adjuncts if available.
- Wound biopsy is the gold standard for diagnosing infection if suspected.

List of imaging techniques

- CSR when there is concern for inhalation injury.
- Laser Doppler imaging when clinical assessment is inadequate to assess burn extent.
- Bronchoscopy or laryngoscopy should be used for airway injury.

Potential pitfalls/common errors made regarding diagnosis of disease

- Tendency to focus on burn injury instead of triaging for all immediately life-threatening injuries via ABCs.
- Inadequate history.
- Failure to recognize airway injuries or potential for expansion of injury as edema increases following resuscitation.

Treatment

Treatment rationale

- In general, superficial burns can be managed conservatively.
- Second degree or greater burns will require medical attention.
- During triage, two large bore IVs should be placed for early resuscitation in case it becomes apparent resuscitation will be necessary, and amount can be determined using the Parkland formula.

Table 38.1 Burn classification.

Classification	Histologic level	Clinical characteristics	Healing time/method
First degree (partial)	Epidermis	Blanching erythema, tender	2–4 days/sloughed epidermis replaced by regenerating keratinocytes
Second degree superficial (partial)	Superficial (papillary) dermis	Blanching erythema, moist with blistering, extremely tender	1–2 weeks/epidermis regenerates from dermal appendages
Second degree deep (full)	Deep (reticular) dermis	White intermixed with erythema, less blanching, drier with potential blood blisters, less and variably painful	3–4 weeks/regeneration from wound edges as appendages are lost, scarring is typical, often managed surgically
Third degree (full)	Subcutaneous	White or charred with eschar, dry and leathery, non-blanching, insensate	Variable, managed surgically
Fourth degree (full)	Muscle or bone	Charred with eschar, insensate	Variable, managed surgically

- Patients with concerning airways or with significant injuries meeting transfer criteria should be intubated or transferred to a burn center, respectively.
- Succinylcholine should not be used to intubate a burn patient if intubating after 72 hours because of the risk of severe hyperkalemia.
- Prophylactic systemic antibiotics should be avoided as they have not been shown to lower risk of invasive wound infections.
- Efforts should be made to initiate early enteral feeding as management of nutrition is critical to healing. TPN should be avoided as it has been shown to increase mortality in burn patients.
- Circumferential deep burns should undergo urgent escharotomy.
- Blisters >2 cm should be gently debrided and inspected.
- Wound treatment is geared towards limiting loss of additional tissue, preventing bacterial invasion, and decreasing evaporative losses.
- Superficial partial wounds should be treated with topical antimicrobials with attempts to minimize painful dressing changes.
- Deep partial thickness wounds can be treated similarly if small.
- In larger wounds and in full thickness burns, the wound should be excised and covered with autologous, meshed, split thickness skin graft or non-meshed material if in a cosmetically sensitive area.
- If wounds are too extensive for autologous grafting, skin substitutes may be used.
- Optimal timing of burn wound excision is within 48 hours to minimize risk for infection and expedite hospital stay and can be accomplished in a single or staged manner if the burn area is large or donor site scarce.

When to hospitalize

- Partial thickness burns greater than 10–20% TBSA, with a lower threshold for transfer in patients younger than 10 or older than 50 years.
- Burns that involve the face, hands, feet, genitalia, perineum, or major joints.
- Third degree burns in any age group.
- Electrical burns, including lightning injury.
- Chemical burns.
- Inhalation injury.
- Burn injury in patients with pre-existing medical disorders that could complicate management, prolong recovery, or affect mortality.
- Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient may be initially stabilized in a trauma center before being transferred to a burns unit. Physician judgment will be necessary in such situations and should be in concert with the regional medical control plan and triage protocols.
- Burned children in hospitals without qualified personnel or equipment for the care of children should be moved to hospitals with specialist facilities.
- Burn injury in patients who will require special social, emotional, or rehabilitative intervention.

Criteria for non-burn center hospital admission

- Partial thickness burn of 5–10% TBSA in patients aged <10 or >50 years.
- Mild to moderate voltage injury.
- Suspected but not definitive inhalation injury.
- Circumferential injury not meeting burn center referral criteria.

Managing the hospitalized patient

- ABCs guide initial urgent management (e.g. intubation for airway concern, hyperbaric or high flow oxygen for carbon monoxide poisoning, urgent escharotomy for circumferential burns).
- Immediate assessment of burn depth and severity with gentle debridement if necessary and pain control.
- Determination of fluid requirements using the Parkland formula and initiation of resuscitation with a goal urine output of 0.5–1 mL/kg.
- Transfer to burn center if indicated.
- Placement of nasogastric tube for prevention of gastric ileus in large wounds.
- Application of topical antimicrobials.
- Application of an appropriate dressing for superficial and partial thickness injuries with biologic or non-biologic antimicrobial dressings.
- Early excision and grafting more extensive burns with autograft, allograft, or dermal substitute.
- Determination of nutrition requirements and early post gastric or parenteral nutrition initiation.
- Medical management to blunt catecholamine surge and catabolic response (commonly propranolol).
- Reassessment of wounds to assess for larger wound conversion and graft take.

Table of treatment

Treatment	Indications (extent of injury) and comments
Conservative	Small superficial burns
Topical therapy	
Bacitracin 500 U/g ointment	Superficial, PT, or grafts, Gram+ cocci
Mupirocin 2% ointment	Superficial, PT, or grafts, active against MRSA
Silver nitrate 0.5% cream	PT, broad coverage
Mycostatin 100 000 U/g ointment	Superficial grafts, fungal coverage only
Silver sulfadiazene 1% cream	DD or FT, intermediate eschar penetration, broad spectrum
Mafenide acetate 11% H_2O soluble cream or 5% solution	DD or FT, excellent eschar penetration, broad spectrum especially against *Pseudomonas*, poor against *Staphylococcus*
Anticoat flexible polyester, polyethylene silver mesh	Broad spectrum, can be left in place for up to 1 week
Aquacel® Ag: methylcellulose ionic silver dressing	PT, can be left in place until healing is complete, requires clean wound for adherence
Biobrane®: silicone collagen blend with nylon surface dressing	PT, can be left in place until healing is complete, reduces evaporative losses
Surgical	
Tangential excision	For PT wounds, to conserve dermal appendages if spared by injury
Complete excision	For DD or FT
Grafting	For significant partial thickness or deeper injuries. Split thickness typically employed acutely, whereas full thickness is usually reserved for post-burn reconstruction if at all. Autografting is ideal. Dermal substitutes can be used to replenish the normal properties of skin following full thickness excision. Allograft, dermal/epidermal substitutes, and cultured skin substitutes used for extensive and/or irregular wounds
Escharotomy	For circumferential burns of chest, extremity, or over joints
Fasciotomy	For compartment release if injury has impaired perfusion to a compartment for 4–6 hours
Local tissue transfer	To release tension and prevent release contracture over a mobile area

DD, deep dermal; FT, full thickness; PT, partial thickness.

Prevention/management of complications

- Over-resuscitation or 'fluid creep' should be monitored because it can rapidly cause pulmonary edema, arrhythmias, compartment syndromes, and conversion of superficial to more extensive wounds.
- Extensive blood loss with tangential excisions is common and can be minimized by operating within 24 hours of injury or applying a tourniquet or local vasoconstrictive agents during the operation.
- Mafenide can cause metabolic acidosis due to carbonic anhydrase inhibition.
- Silver nitrate can cause hyponatremia and methemoglobinemia; the latter can be treated with methylene blue.
- Silver sulfadiazine can cause neutropenia.

CLINICAL PEARLS

- Immediate and aggressive crystalloid fluid resuscitation and correction of electrolytes is imperative in maintaining homeostasis in the burn patient, and physiologic response should be monitored closely during the hospital course.
- A thorough baseline assessment of the extent of injury is important for monitoring progression and treatment.
- Judicious use of topical antibacterial medications and semi-occlusive dressings should be used to minimize the risk of infection, fluid loss, and worsening of injury.
- Early excision of burn wound and definitive closure should be accomplished as early as possible to limit the likelihood of complications and improve long-term outcome.

Special populations

Children

- Burn is a common injury in children, in 2006 ranking third among unintentional causes of death. Burn management in children differs from that in adults in several ways.
- Children contain proportionally more surface area in their head and neck (approximately 21% in infancy) and less in their legs (approximately 13% in each leg), which alters the TSBA calculation.
- One method of adjusting for age is to subtract 1% from the head and neck and add 0.5% to each leg for each year over 1 using the typical rule of nines.
- Due to an underdeveloped renal system, children are less able to concentrate urine so resuscitation monitoring is especially important.
- Target urine output is 1–2 mL/kg/h instead of 0.5–1 mL/kg/h in adults.

Others

Patients with electrical burn injuries

- Electrical burns account for about 5–10% of all burn center admissions but are an important cause of significant injuries, amputations, and mortality (see Figure 38.2).
- Unlike other types of burn injuries, electrical energy tends to disperse deep to the skin and the superficial appearance may or may not be indicative of the true extent of injury.
- Neurologic, cardiac, and respiratory consequences occur; deep tissue tends to retain heat and dissipation around bone occurs slowly; and muscle injury is a commonly documented complication.
- Urine monitoring is particularly important as muscle injury leading to myoglobinuria can lead to acute tubular necrosis and renal failure.
- TBSA is inaccurate so the Parkland formula does not apply.
- Urine output should be titrated to at least 1 mL/kg/h with consideration for urine alkalinization if myoglobinuria is significant.
- All patients with concern for significant electrical injury should be transferred to a burn unit as rapid deterioration can occur.

Patients with chemical burn injuries

- Chemical burns are a relatively uncommon injury and cause for transfer to a burn unit but can have devastating consequences nonetheless.
- Alkali causative agents are known to cause the most severe injuries via cellular dehydration, saponification, and liquefaction necrosis.
- Regardless of the agent, the key to effective early management is removal of the caustic agent.
- All clothing should be removed, the agent should be swept off the skin, and copious amounts of water should be used to dilute it.
- Neutralizing agents should be avoided.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Prognosis following a burn injury is multifactorial and variable.
- With early treatment the majority of patients survive with or without disfiguring scar tissue.
- Monitoring of electrolytes and nutritional parameters and scar evolution should continue following hospital discharge as these processes may not stabilize for several years.

Natural history of untreated disease

- The prognosis for untreated disease is widely variable and dependent on depth, extent, and location of injury as well as the ability of the victim to tolerate the pathophysiologic consequences and complications.
- With or without treatment, approximately 75% of patients with burns covering >80% TBSA die.
- A Baux score (age + %TBSA) has shown to correlate with mortality, with a score of 160 indicative of nearly 100% mortality and 109 indicative of d50 (score at which 50% experience mortality).
- Population-based studies in countries without modern medical infrastructure suggest that the overall prognosis of burn injury is fair with >80% of all burns resolving without significant complications and a death rate of 1–5%.

Prognosis for treated patients

- Prognosis of treated disease is similarly variable; however the majority of literature suggests rapid wound closure and incidence of infection and other complications is substantially reduced when the burn wound is excised within 48 hours.
- The vast majority of those treated will ultimately survive with a wide range of disability.

Follow-up tests and monitoring

- The hypermetabolic, hypercatabolic effects of burn can persist for up to 3 years.
- Basic assessment of electrolyte, glycemic control, and overall nutrition should periodically be reassessed during this time.
- Hypertrophic scarring is a common complication and can be quite disfiguring.
- Scar maturation is a slow process and many parties advocate delaying reconstruction operations for 1–2 years following injury.
- The evolution of these scars should be monitored particularly if they are in areas of mobility to ensure joint contractures do not occur; targeted exercise can inhibit this process.
- Long-term psychosocial support is helpful in coping with the injury.

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Suggested websites

http://www.aafp.org/afp/2000/1101/p2015.html#sec-1

Ameriburn.org

http://kallus.com/er/calculations/parkland.htm

Guidelines (H1)

National society guidelines

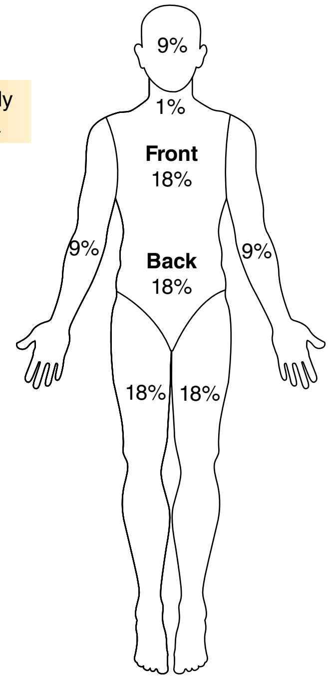
Title	Source	Date and weblink
Burn Center Referral Criteria	American Burn Association	2006 http://www.ameriburn.org/ BurnCenterReferralCriteria.pdf

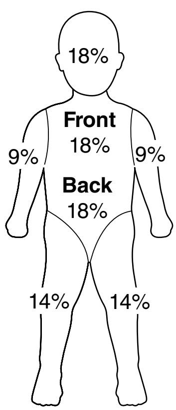
Evidence

Type of evidence	Title and comment	Date and reference
Systematic review of RCTs	*Meta-analysis of Early Excision of Burns* Demonstrates reduction in mortality in early burn surgery	2006 Ong Y, Samuel M, Song C. 2006;32(2):145–50
Systematic review of RCTs	*Antibiotic Prophylaxis for Preventing Burn Wound Infection* Demonstrates lack of evidence to support use of systemic antibiotics for prophylactic treatment of burn	2013 Barajas-Nava L, López-Alcalde J, Roqué i Figuls M, Solà I, Bonfill Cosp X. Cochrane Database Syst Rev 2013;6(6):CD008738.
RCT	*Failure of TPN Supplementation to Improve Liver Function, Immunity, and Mortality in Thermally Injured Patients*	1987 Herndon D, Stein M, Rutan T, Abston S, Linares H. J Trauma 1987;27(2):195–204

Images

Adult body part	% total of body surface area
Arm	9%
Head	9%
Neck	1%
Leg	18%
Anterior trunk	18%
Posterior trunk	18%





Child body part	% total of body surface area
Arm	9%
Head and neck	18%
Leg	14%
Anterior trunk	18%
Posterior trunk	18%

Figure 38.1 Rule-of-nines for assessment of total body surface area (excludes first degree burns).

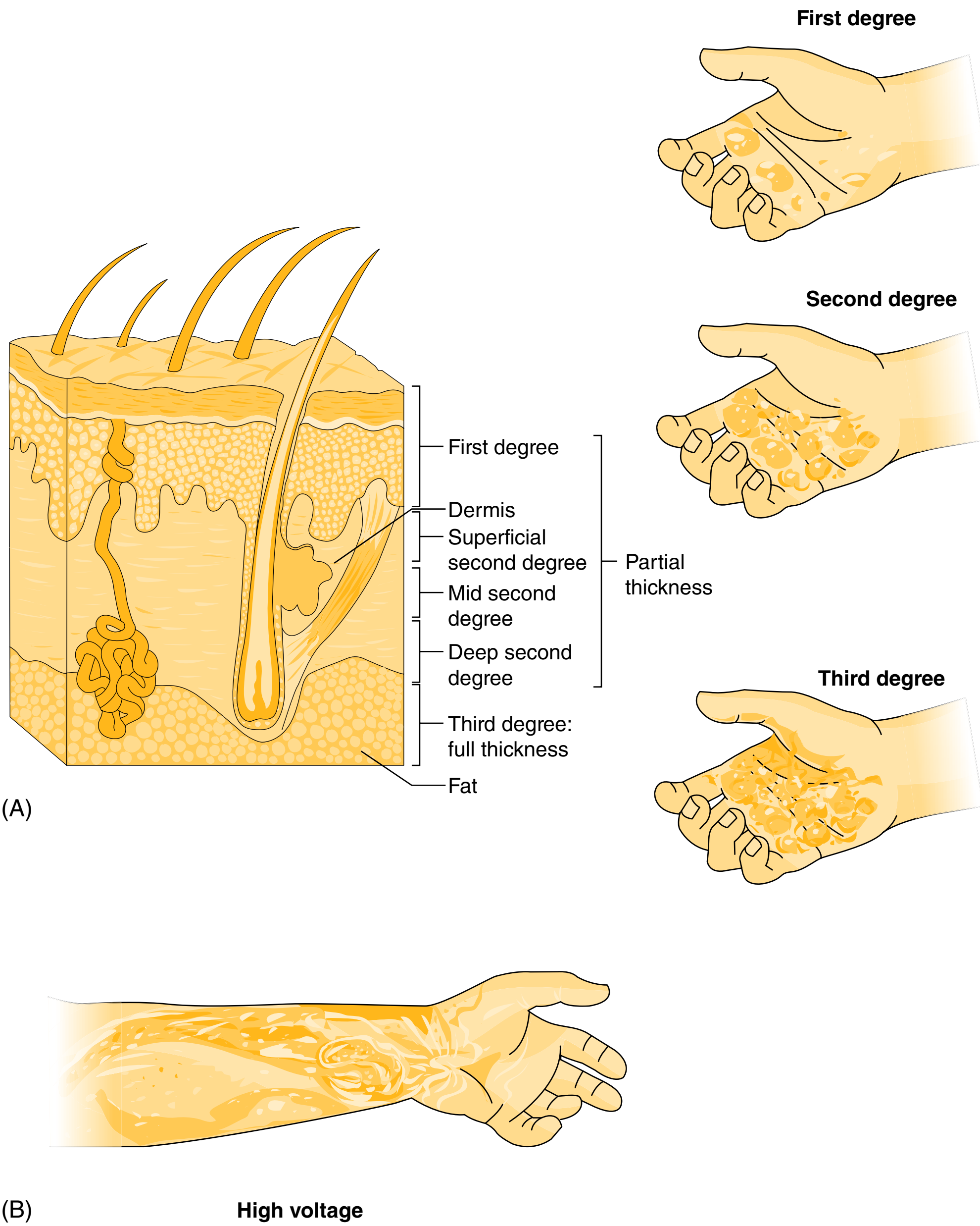


Figure 38.2 (A) Clinical findings in first, second, and third degree burns and (B) high voltage burn.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 39

Acute Hepatic Failure

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OVERALL BOTTOM LINE

- The underlying cause of liver failure and the grade of the encephalopathy at time of presentation are critical determinants of outcome.
- Drug-induced hepatitis and viral hepatitis are the most common cause of acute liver failure.
- Hepatic encephalopathy is a defining characteristic of acute liver failure.
- Supportive care with removal of the primary cause is the mainstay of treatment. Liver transplantation may be considered when spontaneous survival is considered unlikely.

Background

- Acute hepatic failure (AHF) is a rare but life-threatening critical illness seen most commonly in previously healthy young adults without any pre-existing liver disease.
- Survival rates have improved substantially in recent times, through advances in emergency liver transplantation and acute care management.

Definition of disease

- Acute hepatic failure is generally defined as findings of abnormal liver function tests (LFTs) along with an elevated INR >1.5 and signs or symptoms of hepatic encephalopathy (HE), in a patient with no known previous liver disease.

Disease classification

- Depending on the time of presentation, hepatic failure can be classified as follows:
  - Hyperacute (<7 days).
  - Acute (7–21 days).
  - Subacute (21 days to 26 weeks).
  - Chronic (>26 weeks).
- Fulminant hepatic failure is a term used to describe rapidly progressing liver failure that develops within 8 days of the onset of symptoms and signs of liver failure.

Incidence/prevalence

- In the USA, 2000 cases of AHF occur yearly, accounting for up to 6% of all liver-related deaths.
- The majority of cases are observed in women (67%) with a mean age of 38 years (range 17–79 years).

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Etiology

- Globally, drug-induced hepatitis and viral hepatitis are the most common causes of AHF, whereas, in the USA, the most common cause of AHF is acetaminophen toxicity.
- The causes of AHF can be categorized as:

Drugs	Acetaminophen (dose dependent); risk is greatest with ingestion staggered over hours or days rather than at a single large dose) Alcohol Recreational drugs (MDMA/ecstasy, cocaine) Toxins (*Amanita phalloides*, carbon tetrachloride from solvents, herbal supplements (kava, ephedra)) Idiosyncratic drug reaction (typically dose independent unlike acetaminophen); can be caused by several common drugs such as antibiotics, NSAIDs, and anticonvulsants which result in drug-induced liver injury
Infections	Hepatitis A and E are the major causes of AHF Other viral infections include hepatitis B, cytomegalovirus, herpes simplex, varicella zoster, and adenovirus
Vascular	Acute ischemic hepatocellular injury or hypoxic hepatitis may occur in the setting of shock or respiratory failure Other vascular causes are Budd–Chiari syndrome and portal vein thrombosis
Metabolic	Wilson's disease
Autoimmune	Autoimmune hepatitis
Miscellaneous	Hemophagocytic lymphohistiocytosis Obstetric syndrome of HELLP (hemolysis, elevated liver enzymes, low platelets)
Idiopathic	

Pathology/pathogenesis

Hepatic failure, whether acute or chronic, leads to a final common pathway that involves reduced clearance of ammonia and lactic acid, reduced gluconeogenesis, and reduced protein synthetic function (Figure 39.1).

Predictive/risk factors for AHF

- Chronic alcohol abuse. Malnutrition. Age >40 years and female sex. Chronic use of pain medication. Pregnancy.

Diagnosis

Differential diagnosis of hepatic failure

Differential diagnosis	Features
Wilson's disease	Neurologic manifestations such as dysarthria, dystonia, tremors, or parkinsonism. Coombs-negative hemolytic anemia, AST to ALT ratio of >2, normal alkaline phosphatase, elevated serum ceruloplasmin level
Acute severe hepatitis	Presentation may be similar to AHF, but typically lacks features of hepatic encephalopathy

Clinical diagnosis

History

- Ingestion history: medication use (prescription/OTC/supplement) with the amount and duration since ingestion, mushroom ingestion, alcohol ingestion.
- Travel to endemic region for hepatitis infection.

- Sexual exposure history.
- History of suicide depression.
- History of malignancy, prior liver disease, family history of liver disease.
- History of blood transfusion.
- For hospitalized patient: history of hypotension/shock, medication used, cardiac function.

Physical examination

- Neurologic: asterixis (flapping tremor/reverse myoclonus), mental status changes, altered sleep cycle secondary to HE. Increased ICP can be manifested as Cushing's triad (systemic hypertension, bradycardia, irregular respirations).
- Fetor hepaticus.
- Skin: jaundice (common but may be absent in early stages), rash/vascular lesions (from infectious, autoimmune causes), petechiae, ecchymosis.
- Eyes: icterus, Keyser–Fleischer rings (in Wilson's disease), pupillary changes due to HE (varies from hyper-responsive in grade II/III HE, to slow responsive in grade IV HE, to fixed dilated in brainstem herniation).
- Cardiovascular: bounding pulses with wide pulse pressure are suggestive of increased cardiac output. Jugular vein distension and holosystolic murmur of tricuspid regurgitation may be observed in congestive hepatopathy.
- GI: abdominal tenderness in right upper quadrant, hepatosplenomegaly, ascites.

Useful clinical decision rules and calculators

- MELD (model for end-stage liver disease) score:
  - www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older.
  - Calculated from creatinine, bilirubin, and INR, with correction for sodium, which is used for chronic liver failure.
  - MELD is also used as a prognostic model to predict short-term mortality risk and to prioritize patients on the transplant list for acute hepatic failure.
- King's College criteria for acetaminophen toxicity:
  - www.mdcalc.com/kings-college-criteria-acetaminophen-toxicity.
  - This is another predictive model based on which acute liver failure patients are referred for orthotropic liver transplantation.
  - The factors used are different for different etiologies (acetaminophen versus other causes).
- West Haven Hepatic Encephalopathy Scale:
  - Grade I: changes in behavior, mild confusion, slurred speech, disordered sleep.
  - Grade II: lethargy, moderate confusion.
  - Grade III: marked confusion (stupor), incoherent speech, sleeping but wakes with stimulation.
  - Grade IV: coma, unresponsiveness to pain.

Laboratory diagnosis

List of diagnostic tests

- Routine blood: CBC, CMP, LFTs, coagulation panel.
- Hepatitis panel, viral serology testing, ammonia.
- Toxicology screen and acetaminophen level.
- Autoimmune investigation: ANA, anti–smooth antibody, anti-LKM antibody.
- Ceruloplasmin level in suspected Wilson's disease.

List of imaging techniques

- Abdominal ultrasound: for diagnosis of cirrhosis, Budd–Chiari syndrome, and other vascular diseases.
- CT/MRI/magnetic resonance venography: if malignancy is suspected or ultrasound is negative.

Treatment

Treatment rationale

- Grade I hepatic failure can be managed on the medical floors/wards.
- HE that progresses to grade II and beyond, typically requires ICU level of care.

Managing the hospitalized patient

Laboratory monitoring

- CBC: monitor anemia.
- Comprehensive metabolic panel and electrolytes every 6 hours: to monitor creatinine/BUN, serum amylase, lipase, electrolyte imbalance (hypokalemia, hypomagnesemia, hypophosphatemia) along with hypoglycemia.
- LFTs (daily): improving liver enzymes could be misleading as it can indicate improving liver function versus loss of hepatic mass.
- Coagulation panel: to monitor PT/INR as prognostic factors. Plasma transfusion should be avoided unless there is a compelling indication to do so.
- Blood gas analysis: for acid–base disorder (alkalosis more common than acidosis initially).
- Ammonia: serum ammonia <75 μg/dL rarely causes HE. Arterial ammonia >100 μg/dL is an independent risk for intracranial hypertension, and >200 μg/dL predicts intracranial hypertension.

General systemic management strategies

- *Hemodynamic stability*:
  - The goal is a MAP of 75 mmHg or cerebral perfusion pressure (CPP) 50–60 mmHg to avoid cerebral hypoperfusion and anoxia.
  - For patients who are hypotensive or volume depleted, give fluid resuscitation with NS or 1/2NS + HCO_3 if acidotic.
  - Dextrose for hypoglycemia.
  - Norepinephrine is the preferred initial vasopressor; the second choice would be vasopressin.
- *Bleeding management*:
  - With liver failure both pro- and anticoagulant factor synthesis are impaired. Bleeding risk is overestimated with conventional tests like PT/INR. Therefore, fibrinogen levels and thromboelastography are better to guide transfusion therapy instead of a simple coagulation panel.
  - FFP transfusion is not recommended. Transfusion is typically reserved for bleeding episodes or planned procedures (like ICP monitor placement).
  - Proton pump inhibitors should be given for GI prophylaxis.
- *Neurologic support*:
  - The goal is to prevent the onset or progression of HE and cerebral edema.
  - ICP monitoring, avoiding agitation, and maintaining fluid balance are the main goals.
  - Once intracranial hypertension develops, the definitive therapy is liver transplantation, because cerebral edema is irreversible with medical therapy alone.
  - Until transplantation can occur, an elevated ICP should be treated with bolus osmotherapy, with repeated doses as needed:
    - IV hypertonic saline: 30 mL of 23.4% sodium chloride or 200 mL of 3% sodium chloride.
    - IV mannitol at a dose of 0.5–1.0 g/kg 20% solution.
  - Temperature goal is hypothermia 32–34°C.
  - Hyperventilation (which results in vasoconstriction and a reduction in ICP) and barbiturate anesthesia are last resorts if all the above therapy fails.
  - Lactulose has no proven benefit in HE in acute liver failure.
- *Infection control*:
  - Patients with compromised liver function are at very high risk of developing infections. Immunization and early treatment of infections is essential.

- *Renal management*:
  - Renal failure is associated with increased mortality and is most prevalent in elderly patients and patients with acetaminophen toxicity.
  - If renal replacement therapy is needed, continuous veno-venous hemofiltration is advised over intermittent dialysis. In most cases, renal function returns to baseline with resolution of liver failure.
- *Nutritional support*:
  - Patients with acute liver failure are in a catabolic state and require nutritional support. In encephalopathy, enteral protein of 1.0–1.5 g/kg/day is advised.

Specific management

- *N-acetyl cysteine*: mainly used for acetaminophen toxicity. Can also be used for patients in whom acetaminophen is suspected as a contributing factor or cases where the cause is undetermined.
- *Liver transplantation*: patients who do not recover spontaneously from acute liver failure require liver transplantation as definitive therapy. In the USA, patients with AHF requiring liver transplantation are given highest priority in the transplant list. Scoring systems like MELD and the King's College Criteria are used to optimize organ allocation.
- *Steroids*: antiviral regimen for the treatment of hepatitis B and acyclovir for the treatment of herpes virus infection are beneficial.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- The overall mortality rate for fulminant AHF is about 30%.
- Approximately 45% of patients recover spontaneously without liver transplantation and 25% of cases require liver transplantation.
- The main predictors of liver transplantation are the primary cause of AHF, age of the patient, and degree of hepatic encephalopathy.

Prognosis for treated patients

- The 1 year survival rate following liver transplantation is approximately 80%.

Reading list

Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. Clin Liver Dis 2013;17:587.
Gill RQ, Sterling RK. Acute liver failure. J Clin Gastroenterol 2001;33:191–8.
Lee WM. Etiologies of acute liver failure. Semin Liver Dis 2008;28:142.
Stravitz RT. Critical management decisions in patients with acute liver failure. Chest 2008;134:1092.

Guidelines

National society guidelines

Title	Source	Date and weblink
Acute Liver Failure, Management	American Association for the Study of Liver Diseases	2011 https://www.aasld.org/publications/practice-guidelines
American Gastroenterological Association Institute Guidelines for the Diagnosis and Management of Acute Liver Failure	American Gastroenterological Association	https://www.gastrojournal.org/article/S0016-5085(16)35540-8/abstract

Image

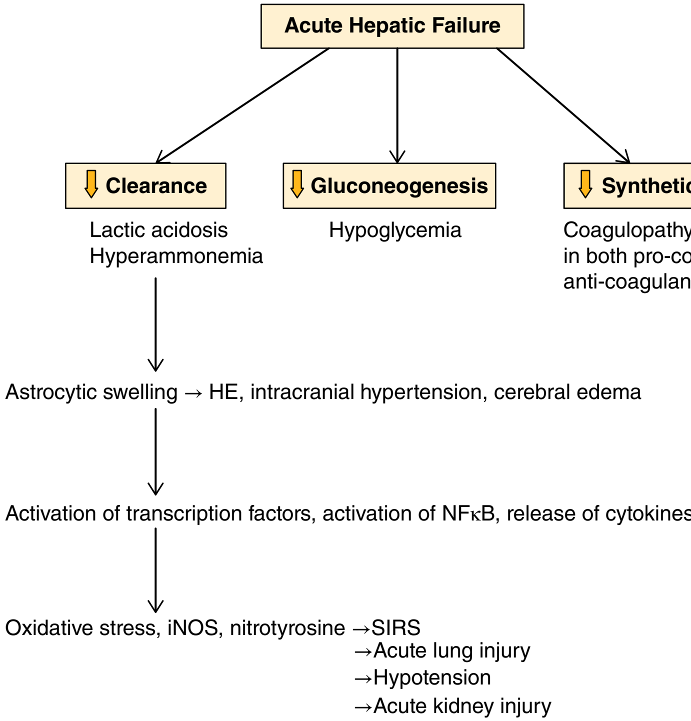

Figure 39.1 Pathomechanisms involved in hepatic failure.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 40

Abdominal Organ Transplantation

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OVERALL BOTTOM LINE

- The most common liver transplant technique is orthotopic transplantation, in which the native liver is removed and replaced by the donor organ in the same anatomic position as the original liver. The surgical procedure is complex, requiring careful procurement of the donor organ and meticulous implantation into the recipient.
- Kidney transplantation is definitive treatment for eligible patients with end-stage renal disease (creatinine clearance <20 mL/min) regardless of the primary cause.
- Intestinal transplant is a therapeutic option for patients with intestinal failure, defined as the inability to maintain sufficient electrolyte, nutrient, and fluid balance for >1 month without TPN.
- Glucocorticoids (most often methylprednisolone in the ICU setting), tacrolimus (FK506), a calcineurin inhibitor, and mycophenolate mofetil are the mainstay agents for immunosuppression in solid organ transplantation.

Liver transplantation

Background

- Orthotopic liver transplantation (OLT) is the treatment of choice for selected patients with end-stage liver disease and acute liver failure.
- The first human OLT was performed by Dr. Thomas Starzl in 1963.
- With the development of surgical techniques and the introduction of newer and more effective immunosuppressive medications, survival has now reached 70–80% at 5 years.
- Organ allocation has also evolved over time, with the current system based upon the model for end-stage liver disease (MELD) score (see Chapter 39), prioritizing patients based upon the severity of their disease and likelihood of death without transplantation.
- Non-cholestatic cirrhosis is the most common diagnosis of patients on the waiting list for liver transplantation.

Indications and contraindications

With improvement in medical and surgical techniques, conditions prohibiting transplantation have decreased over time, and most contraindications have become relative rather than absolute.

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Indications

Indication	Cause of condition
Acute liver failure	Toxins and drugs Acute viral hepatitis Wilson's disease, autoimmune hepatitis, Budd–Chiari syndrome
Chronic decompensated liver failure:	
Non-cholestatic diseases	Hepatitis B/C Alcoholic liver disease Non-alcoholic steatohepatitis Budd–Chiari syndrome Autoimmune hepatitis Polycystic liver disease
Cholestatic diseases	Primary biliary cirrhosis (PBC) Primary sclerosing cholangitis (PSC) Secondary biliary cirrhosis Biliary atresia Alagille syndrome
Metabolic conditions causing systemic disease	Primary oxaluria Familial amyloidosis Alpha-1 antitrypsin deficiency Wilson's disease Hemochromatosis Urea cycle enzyme deficiencies Glycogen storage disease
Malignant disease	Hepatocellular carcinoma Hepatoblastoma Cholangiocarcinoma Neuroendocrine carcinoma Epithelioid hemangioendothelioma

Contraindications

Relative contraindications	
Age >70 years	Assessment of overall health and performance status
Severe malnutrition or morbid obesity	Associated with poor outcome, technical challenges
Other organ failure	Consideration for multiorgan transplantation
Complex previous upper abdominal surgery	Not technically feasible
Poor functional status	Associated with poor outcome
Poor medical compliance	Unlikely to comply with immunosuppression

(*Continued*)

Absolute contraindications	
Severe cardiopulmonary disease	Heart/lung disease that would prevent a successful operation
Irreversible cerebral injury	Elevated intracranial pressure unresponsive to treatment
Sepsis/active infection	Severe uncontrolled systemic infection
HIV/AIDS	Untreated AIDS, unresponsive to treatment
Extrahepatic malignancy	Disease-free period of <2 years depending on the type of malignancy
Vascular	Anatomic variations, extensive portal and mesenteric vein thrombosis leading to technical difficulties
Active chronic alcohol and drug usage	Required abstinence for a minimum of 6 months
Psychosocial issues	Severe disorder, lack of social support

Techniques

Whole liver recipient procedure

- Step 1: total hepatectomy via bilateral subcostal incisions with or without midline extension to the xiphoid process.
- Step 2: assessing the need for veno-venous bypass. This involves the extracorporeal circulation of blood from the venous system below the caval clamps (inferior mesenteric and femoral veins) and return to the central veins (axillary or internal jugular veins). This procedure is, however, associated with major complications (up to 30%) including lymphocele, hematomas, coagulopathies, plexus injury, and fatal pulmonary emboli. Relative indications of the use of veno-venous bypass are pulmonary hypertension, poor left ventricular function, fulminant hepatic failure, renal failure, severe portal hypertension, and massive bleeding during the hepatectomy.
- Step 3: implantation and caval techniques:
    - Standard technique with caval replacement (Figure 40.1): requiring anastomosis of supra- and infrahepatic cava.
    - Piggyback technique (Figure 40.2): this technique avoids caval cross clamping and preserves the retrohepatic native IVC. It helps maintain IVC flow during the anhepatic phase, therefore preserving venous return to the heart and minimizing effects related to full clamping. Potential additional advantages that have been described with this technique are reduction of renal dysfunction, reduced warm ischemia time, and less bleeding.
- Step 4: portal reconstruction: end–end anastomosis or graft to native superior mesenteric vein (retrogastric/retrocolic).
- Step 5: arterial reconstruction: end–end anastomosis or arterial graft to native aorta (retrogastric/retrocolic).
- Step 6: biliary reconstruction: duct-to-duct with/without T-tube or Roux-en-Y hepaticojejunostomy.

Special considerations and technique

- Pre-existing portal vein thrombosis: partial vein thrombectomy or donor iliac vein grafts from the superior mesenteric vein (tunneled retrogastric/retrocolic).
- Hepatic artery dissection or inadequate flow: donor interposition graft to native aorta (retrogastric/retrocolic).
- Pre-existing transjugular intrahepatic portosystemic shunt (TIPS): incision of the pericardium and intrapericardial control of the suprahepatic cava may be necessary to remove TIPS that extends into the heart.

Partial liver recipient procedure

- This includes reduced size, split, and living donor liver transplantation.
- The piggyback technique is mandatory.
- The actual splitting can be performed ex vivo or in situ in a manner analogous to living donor liver transplantation, at the discretion of the surgeon performing the procedure.

Immunosuppression

- Tacrolimus (FK506), a calcineurin inhibitor (CNI) is used as the first line drug in OLT.
- Corticosteroids have been the mainstay for induction of immunosuppression.
- Antimetabolites such as mycophenolate mofetil (MMF) are used in combination with steroids and CNIs to reduce CNI-related renal insufficiency and to prevent rejection.

Complications

Early complications	Hemorrhage Primary non-function Early graft dysfunction Acute cellular rejection Hepatic artery or portal or hepatic vein thrombosis Biliary stricture or leak Infections (bacterial, viral, fungal)
Late complications	Recurrence of disease (HCV, HBV, NASH, autoimmune disease) Chronic rejection Biliary strictures Metabolic syndrome (hypertension, dyslipidemia, diabetes, coronary disease) Malignancies (skin, post-transplant lymphoproliferative disorder) Immunosuppressive side effects

Outcomes

- Two, 5, and 10 year survival in patients undergoing transplantation is 94%, 79%, and 60%, respectively.
- Graft survival at 2, 5, and 10 years is 87%, 75%, and 59%, respectively.
- Recurrence of disease is an important determinant of survival as some conditions do not recur after transplant, while others may recur.

Kidney transplantation

Background

- The first successful kidney transplant was with a living donor between identical twin brothers in 1954.
- With the development of 6-mercaptopurine, followed by azathioprine in the early 1960s, and implementing the use corticosteroids, the medical community has witnessed great advances in patient and graft survival rates in kidney transplantation.
- As knowledge of the immune system evolved, the first polyclonal antilymphocyte globulin was used in 1967, ciclosporine was introduced in 1980s, followed by the introduction of MMF and tacrolimus in 1990s in kidney transplantation.
- Kidney transplantation, depending on the source of the donor organ, is classified as deceased donor/cadaveric or living donor transplantation.
- Living donors are genetically related (living related) or non-related (living unrelated), depending on whether a biologic relationship exists between the donor and recipient.
- Currently, there are over 120 000 people waiting for a life-saving organ transplant in the USA, among whom about 100 000 are on the kidney transplant waiting list.

Indications and contraindications

Kidney transplantation is definitive treatment for eligible patients with end-stage renal disease (ESRD) (creatinine clearance <20 mL/min) regardless of the primary cause.

Indications	Contraindications
Chronic glomerulonephritis	Chronic illness with life expectancy of less than 1 year
Systemic arterial hypertension	AIDS untreated or unresponsive to treatment
Fabry's disease	Sepsis
Hyperoxaluria	Advanced cardiovascular disease
Diabetes mellitus	Poor respiratory status
Unknown renal insufficiency	Cancer (active/unresolved)
Obstructive and toxic uropathy	Psychosocial
Alport's syndrome	
Polycystic kidney disease	
Nephrotic syndrome	
Chronic obstructive pyelonephritis	
Lupus nephritis	
Focal segmental glomerulosclerosis	

Technique

- Regardless of the donor type, the kidney transplant operation is the same.
- The standard kidney transplant procedure with heterotopic pelvic approach has been widely accepted for its multiple advantages and is considered the standard (Table 40.1).

Table 40.1 Liver transplant procedure.

Procedure	Important points
Approach	Extraperitoneal approach of the iliac fossa Contralateral or ipsilateral fossa Lymphostasis to avoid lymphocele Total mobilization of the external iliac vein Minimal dissection of the iliac artery
Vascular anastomosis	Generally external iliac vessels Internal iliac should not be used except in specific situations
Ureteral anastomosis	Extravesicular implantation at the anterolateral surface of the bladder is the method of choice Double J stenting prevents major urinary complications Utero-ureteral anastomosis is an alternative to a very short or poorly vascularized transplant ureter

(Continued)

Table 40.1 (*Continued*)

Procedure	Important points
Kidneys from donor <15 kg	En bloc transplantation including aorta and IVC The ureters are implanted either separately or after partial anastomosis using an extravesical technique
Special considerations	If the iliac arteries do not allow clamping, endarterectomy or vascular prosthesis should be considered If the iliac vein/vena cava is thrombosed, the native renal vein or SMV can be used

Complications

Early complications	Late complications
Acute rejection/acute renal failure	Ureteral stenosis
Infection	Reflux and acute pyelonephritis
Hemorrhage	Kidney stones
Incisional hernia	Renal artery stenosis
Urinary fistula	AVF and pseudoaneurysms
Arterial thrombosis	Lymphocele
Venous thrombosis	Chronic allograft dysfunction
Delayed graft function	Recurrent disease
	Malignancy

Immunosuppression

- Immunosuppressive drugs are started in the operative room with thymoglobulin (2 mg/kg) and methylprednisolone (500 mg) to suppress the immune system from rejecting the donor kidney.
- Thymoglobulin (2 mg/kg) is given on postop day 1 and 2 to complete a total dose of 6 mg/kg. Steroids are tapered and withdrawn after 3 days. In high risk patients the steroid is tapered and maintained for at least 1 year. Note that a number of transplant programs utilize non-depleting antibody induction in the form of basiliximab 20 mg IV intraoperatively and on postop day 4.
- Tacrolimus and MMF are started on postop day 1.

Graft survival

- One year survival (living donor): 99%.
- Three year survival (living donor): 91%.
- One year survival (deceased donor): 88%.
- Three year survival (deceased donor): 77%.

Pancreas transplantation

Background

- Since the first pancreas transplant performed in 1967, there have been over 1200 pancreas transplants performed annually in the USA.

- In most cases, pancreas transplantation is performed in the setting of type 1 diabetes and ESRD.
- The three main types of pancreas transplantation are:
  - Simultaneous pancreas–kidney (SPK) transplantation (Figure 40.3), where the pancreas and kidney are transplanted from the same deceased donor. Performed in two-thirds of cases.
  - Pancreas after kidney (PAK) transplantation, where the deceased donor pancreas transplant is performed after a living or deceased donor kidney transplant.
  - Pancreas transplant alone (PTA) (type 1 diabetic patient with adequate renal function).
  - Significant improvements in surgical techniques, organ preservation, and anti-rejection protocols have made pancreas transplantation an effective therapy for some diabetic patients, and serves to enhance their quality of life and long-term survival.

Indications and contraindications

- In the majority of, cases, pancreas transplantation is performed in individuals with type 1 diabetes with ESRD and associated complications, such as uremia, retinopathy, progressive neuropathy, and hypoglycemic unawareness.
- Living donor pancreas transplantation represents only 0.5% of pancreas transplants performed. Long-term benefits to the recipient must be balanced against both short and long term risks to donors/recipients before this procedure can be advocated.

Acceptance criteria for pancreas transplantation at Mount Sinai Medical Center

- Patient on insulin with C peptide value ≤2 ng/mL.
- Patient on insulin with a C peptide ≥2 ng/mL and a BMI less than or equal to the Organ Procurement Transplantation Network (OPTN) maximum allowable BMI (currently 28).
- Insulin requirement 0.5 U/kg/day if on dialysis and 0.7 U/kg/day if not on dialysis.
- Pancreas transplant alone indicated for documented frequent and life-threatening hypoglycemic unawareness and preserved renal function (Cr clearance >70).

Contraindications

- Absolute contraindications to pancreatic transplant include untreated infection at the time of transplant, chronic illness with life expectancy of less than 1 year, and active substance abuse.
- Relative contraindications are those which require careful evaluation and possible therapy prior to transplant. These include cirrhosis of the liver (clinical or pathologic diagnosis) and HIV infection (unless the individual is on appropriate medications, has an undetectable viral load, does not have AIDS-related complications, and has a CD4 >200).
- Other contraindications include advanced COPD, severe coronary artery disease, severe congestive heart failure with ejection fraction <20%, and active or recent malignancy (other than superficial skin cancers).
- The candidacy and waiting time for clearance will be discussed on a case-by-case basis for the following conditions: proven habitual medical non-compliance, uncontrolled psychiatric condition, active systemic lupus requiring more than 10 mg/day prednisone, lack of cognitive capacity to make informed decisions, understand procedure, and sign the consent, obesity (where the benefits of transplantation do not outweigh the risks of the procedure), severe peripheral vascular disease, and severe cerebrovascular disease.

Guidelines for acceptance of deceased donor pancreas at Mount Sinai Medical Center

- Donor age <50 years.
- Donor BMI <30.

- There should be no history of active alcohol abuse.
- Total cold ischemia time should be less than 24 hours.
- Preservation of intact pancreato-duodenal arterial arcade, splenic artery, and superior mesenteric artery.

Pancreas donor grading system

- Usable: absence of edema, nodularity, and fatty infiltrate.
- Usable in most cases: mild disease, fat infiltrate <20%, mild nodularity but soft, mild edema.
- Not usable: any of the following factors – fat infiltrate >20%, firm, significant nodularity, significant edema.

Techniques

Categories of pancreas transplant (Table 40.2)

Techniques of exocrine and venous drainage (Tables 40.3 and 40.4)

Immunosuppression

- Pancreas transplant (SPK/PTA) immunosuppression starts with induction protocol of methylprednisolone (10 mg/kg) and thymoglobulin (2 mg/kg; total dose 6 mg/kg) intra-operatively. Methylprednisolone will be switched to prednisone postoperatively and tapered for at least a year in the majority of cases.
- Intravenous immunoglobulin (IVIg) is indicated for patients with either positive CDC or positive T-cell/B-cell flow cytometry cross match as well as patients with donor-specific anti-HLA antibodies. IVIg is given at 1000 mg/kg starting 2 hours before transplantation, 500 mg/kg on postop day 1, and 500 mg/kg on postop day 2.
- The most common regimen used for maintenance immunosuppression includes tacrolimus and MMF as triple therapy in conjunction with prednisone. Steroids may be discontinued after a year in selected patients with a low risk of rejection and stable graft function.

Table 40.2 Advantages and disadvantages of the different types of pancreas transplant.

Category	Advantage	Disadvantage
Simultaneous kidney-pancreas transplant (SPK)	Rejection can be monitored by transplant kidney function Immunosuppresion already needed for kidney transplant Better quality of life	Longer waiting list than pancreas transplant with living donor kidney transplant Increased risk of surgery than kidney transplant alone
Pancreas transplant alone (PTA)	Better quality of life	Rejection should be monitored Life-long immunosuppression Risk of peri-operative morbidity
Pancreas after kidney transplant (PAK)	Better quality of life Immunosuppression already started for previous kidney transplant	Rejection should be monitored Risk of peri-operative morbidity
Simultaneous deceased donor pancreas and living donor kidney	Shorter waiting time Immunosuppression already needed for kidney transplant	Rejection should be monitored Increased risk of surgery than kidney transplant alone
Islet cell transplant	No need for surgery	Lower success rate (insulin independence) Multiple injections may be needed

Table 40.3 Exocrine drainage.

Type of duct management	Advantage	Disadvantage
Bladder drainage	Urinary amylase can be used to monitor for rejection Easier access to pancreas graft for biopsy	Urinary complications (UTI, urethritis, cystitis, hematuria, prostatitis) Metabolic acidosis, dehydration, and electrolyte imbalance
Enteric drainage (ED)	No urinary complications More physiologic	Loss of urinary amylase to monitor rejection Need percutaneous, laparoscopic, or open biopsy to exclude rejection Leak has higher morbidity
ED with Roux-en-Y venting jejunostomy	Endoscopic surveillance and biopsy for pancreas rejection No urinary complication	Extra-abdominal ostomy Leak has higher morbidity
ED with gastro-jejunostomy	Endoscopic surveveilance and biopsy for pancreas rejection No urinary complications	Leak has higher morbidity
ED with duodeno-duodenostomy	Endoscopic surveillance and biopsy for pancreas rejection No urinary complications	Leak has higher morbidity

Table 40.4 Venous drainage.

Type of venous drainage	Technique	Advantage	Disadvantage
Systemic drainage	Graft portal vein anastomosed to the recipient inferior vena cava or external iliac vein	Easier technique Lower rate of graft thrombosis due to high flow systemic system	Not physiologic Hyperinsulinemia Long-term dyslipidemia
Portal drainage	Graft portal vein anastomosed to the recipient superior mesenteric vein	Physiologic	More difficult technique Higher rate of graft thrombosis due to low flow portal system

Complications

Early complications	Late complications
Thrombosis	Urinary tract infections/hematuria
Hemorrhage	Sterile cystitis, urethritis, balanitis
Reperfusion pancreatitis	Metabolic acidosis
Peripancreatic abscess	Reflux pancreatitis
GI bleeding or hematuria	Arterial stenosis (Y graft or native iliac)
Leak (bladder or bowel)	Rejection related
	Complication of biopsy
	Arterial fistulae

Outcomes

Procedure	1 year survival	5 year survival
SPK	86%	74%
PAK	79%	62%
PTA	74%	51%

Small bowel and multivisceral transplantation

Background

- The first case of human bowel transplantation was reported in 1967. The first multivisceral transplantation performed in the USA was in 1987.
- Small bowel transplantation (SBT) is one of the most technically challenging procedures and the least commonly performed solid organ transplantation procedure worldwide.
- SBT can be done as an isolated procedure (47%), combined small bowel/liver (27%), or small bowel/liver combined with other organs, including stomach, pancreas, or kidney (multivisceral transplantation).
- Current survival rates of intestinal transplantation have improved significantly and are similar to other organ transplants.

Indications in adults

- Intestinal transplant (Figure 40.4) is a therapeutic option for patients with intestinal failure, defined as the inability to maintain sufficient electrolyte nutrient and fluid balance for >1 month without TPN.
- Indications for transplantation include intestinal failure and one of the life-threatening complications of parenteral nutrition. These include loss of venous access (thrombosis of two or more central venous access sites), recurrent life-threatening catheter-associated bloodstream infections, frequent episodes of severe dehydration despite TPN and IV fluid supplementation, and the development of intestinal failure-associated liver disease.

Techniques (Table 40.5)

Table 40.5 Intestinal transplant procedures.

	Isolated intestinal graft	Liver and intestine	Multivisceral
Indication	Intestinal failure Catheter-related infections Poor venous access Moderate hepatic dysfunction Severe fluid and electrolyte imbalance that cannot be managed with TPN	Intestinal failure Irreversible hepatic failure or coagulopathy	Thrombosis Anatomic Following extensive surgical resection of abdominal organs for aggressive tumor or severe abdominal trauma
Venous outflow	Portal vein (into IVC or portal vein)	Suprahepatic IVC (hepatic piggyback anastomosis)	Suprahepatic IVC (hepatic piggyback anastomosis)
Arterial inflow	Superior mesenteric artery	Celiac and superior mesenteric artery	Celiac and superior mesentenric artery
Biliary reconstruction	No need	Roux-en-Y hepatico-jejunostomy (no need if graft includes pancreas)	No need (Roux-en-Y if graft does not include liver)
Proximal GI tract	Jejuno-jenunostomy	Jejuno-jenunostomy	Esophago- or gastro-gastrostomy
Distal GI tract	Ileocolostomy with various type of stoma (loop, Mikulicz, Bishop–Koop)	Ileocolostomy with various type of stoma (loop, Mikulicz, Bishop–Koop)	Ileocolostomy with various type of stoma (loop, Mikulicz, Bishop–Koop)

Immunosuppression

- SBT induction immunosuppression starts in the operating room with high dose methylprednisolone (20 mg/kg), and prednisone will be continued at least for a year in a tapering fashion.
- Thymoglobulin (2 mg/kg) is also infused as an induction agent in the operating room and will be repeated for two more doses to achieve a total amount of 6 mg/kg.
- Maintenance immunosuppression begins on postop day 1, with tacrolimus for life.

Complications

- Early complications of SBT are mostly surgical. Anastomosis leak with intra-abdominal infection, graft vessel thrombosis, and bleeding are not uncommon and necessitate surgical exploration.
- Intermediate to late complications include rejection, bacterial and viral infection (EBV, CMV, adenovirus), GVHD, and post-transplant lymphoproliferative disorder.
- Rejection is the most common cause of graft loss and requires immediate biopsy when suspicion arises and treatment.
- Post-transplant lymphoproliferative disorder can manifest between 2 weeks and 6 months after transplantation. Depending on the clinical status, treatment can range from reducing/discontinuing immunosuppression to chemoradiotherapy.

Outcomes

One year survival after isolated intestinal transplantation is 79%.

Reading list

Fishbein TM. Intestinal transplantation. N Engl J Med 2009;361:998–1008.

Kidney Disease: Improving Global Outcomes (KIDGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant Recipients. Am J Transplant 2009;9:S131–55.

Martin P, et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59:1144.

Robertson RP, et al. Pancreas and islet transplantation in diabetes mellitus. Diabetes Care 2006;29:935.

Images

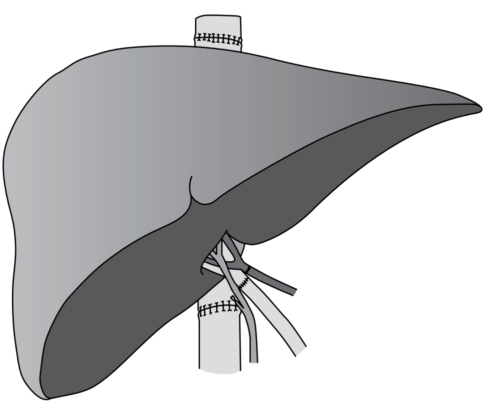

Figure 40.1 Standard liver transplantation technique with caval replacement.

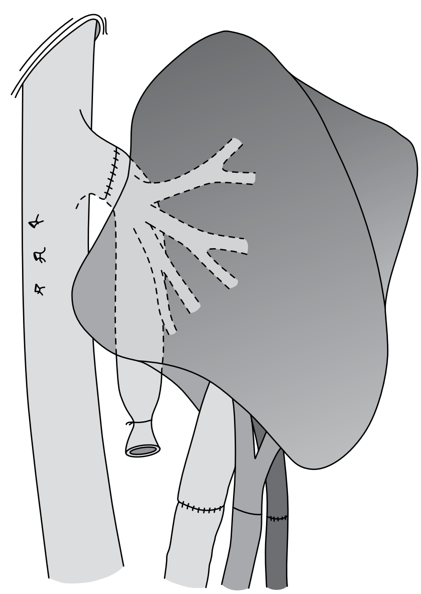

Figure 40.2 Piggyback technique in liver transplantation.

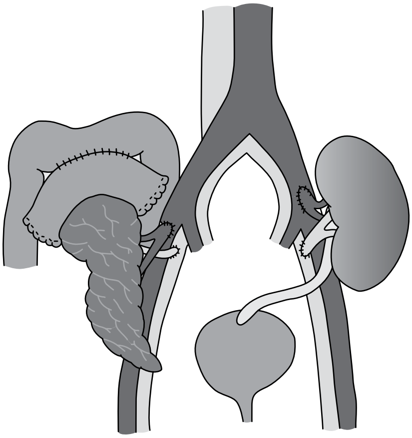

Figure 40.3 Simultaneous pancreas–kidney transplantation.

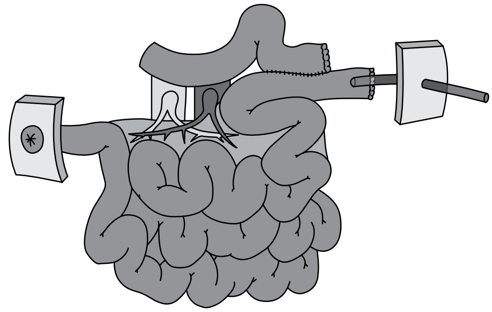

Figure 40.4 Intestinal transplant.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 41

Obstetric Emergencies

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OVERALL BOTTOM LINE

- Pregnancy-induced cardiopulmonary changes affect the management of the critically ill pregnant patient.
- Pregnant patients should be anticipated to have difficult airways.
- Maternal cardiac arrest is rare and tends to be provoked by a potentially reversible cause.
- Amniotic fluid embolus often presents with intra-partum cardiac arrest.
- Pre-eclampsia and eclampsia are caused by endovascular dysfunction which can be mitigated with early treatment and close monitoring.

Overview

Pregnancy results in profound physiologic changes, which are summarized in Table 41.1.

Critical care fundamentals of pregnancy

Airway management

- Incidence of failed airway is seven times greater than in the general population.
- Anticipate difficult airway.

Difficult airway features of the pregnant patient

Category of complication	Specific features
Anatomic	Anterior larynx Mucosal edema Increased aspiration risk
Hypoxemic	Decreased oxygen reservoir Increased oxygen consumption
Hemodynamic	Decreased cardiac reserve Uteroplacental susceptibility to hypotension

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Table 41.1 Physiologic changes in pregnancy.

Affected parameter	Change in pregnancy	Etiology
Cardiac output	Increases 30–50%	Increased SV and HR
SVR and MAP	Decreases	Endogenous vasodilators
Venous return	Decreases	IVC compression by uterus
Uteroplacental blood flow	Increases to 1000 mL/min	Decreased uterine resistance
Pulmonary functional residual capacity	Decreases 10–20%	Increased abdominal pressure
Minute ventilation	Increases 40–70%	Increased respiratory rate
Metabolic profile	$PaCO_2$ decreases; plasma bicarbonate decreases to 17–18 mEq/L	Respiratory alkalosis, chronic metabolic compensation
Oxygen consumption	Increases 20–33%	Fetal O_2 consumption
Glomerular filtration rate	Increases	Increased renal blood flow
Hepatic cytochrome P450 activity	Increases	Hormone mediated

Ventilator management

- Titrate minute ventilation to $PaCO_2$ 30–32 mmHg to prevent fetal hypercarbia.
- Permissive hypercapnia is not indicated.
- Titrate FiO_2 and PEEP to SpO_2 >95% or PaO_2 >70 mmHg to promote fetal oxygenation.
- PaO_2 <60 mmHg leads to fetal hypoxia and decompensation.
- Minimize PEEP to avoid further reductions in venous return leading to hypotension.

Maternal cardiac arrest

Background

Incidence/prevalence

- 1:12 000 admissions for delivery.
- 17.8 deaths per 100 000 live births.

Common causes

- Hypovolemia and hemorrhage.
- Embolic phenomenon.
- Severe pre-eclampsia and eclampsia.
- Sepsis.
- Allergic reactions.
- Medication errors and iatrogenic injuries.
- Anesthetic complications.
- Hypermagnesemia.
- Pre-existing cardiac disorders.

Prevention

- Routine prenatal care.
- Adequate nutrition.
- Vaccination.
- Treatment of pre-eclampsia and eclampsia.
- Optimization of comorbid conditions.

Diagnosis

- History: solicit history of predisposing factors and conditions.
- Physical examination: confirm pulselessness, evaluate airway, auscultate lungs, palpate abdomen, examine extremities, determine gestational age.

- Intra-arrest investigation:
  - Check hematocrit and blood gas.
  - Determine cardiac rhythm.
  - Cardiac ultrasound (POCUS): look for right or left ventricular strain or dilation.
  - Pulmonary ultrasound: look for unilateral absent lung sliding indicating pneumothorax, or B-lines indicating pulmonary edema
  - Abdominal ultrasound: check for free fluid
  - Extremity ultrasound: check for a non-compressible vein indicating deep vein thrombosis.

List of imaging techniques

- Cardiac rhythm monitoring.
- Cardiac ultrasound:
  - Evaluate compression depth/adequacy and location.
  - Evaluate for pulmonary embolism (PE): RV dilation, septal bowing, distended IVC.
  - Evaluate for heart failure: organized contractility with minimal LVEF.
  - Evaluate for tamponade: pericardial effusion with RA or RV diastolic collapse.
- Pulmonary ultrasound:
  - Pneumothorax: loss of lung sliding, stratosphere sign, lung point.
  - Pulmonary edema: confluent B-lines, pleural effusion.
- Abdominal ultrasound:
  - Hemorrhage, placental abruption: abdominal free fluid.
- Extremity ultrasound:
  - DVT: non-compressible femoral, popliteal veins.

Differential diagnosis in maternal cardiac arrest

Differential diagnosis	Features
Amniotic fluid embolus	Rhythm: PEA Intra-partum sudden cardiac death POCUS: systolic dysfunction, RV dilation
Pulmonary embolus	Rhythm: PEA Pre-arrest shortness of breath, chest pain, palpitations, unilateral extremity edema POCUS: RV strain/dilation
Hemorrhage	Rhythm: PEA Hypotension or hemorrhage, palpable abdominal fetus, anemia Cardiac echocardiogram: hyperdynamic LV
Peri-partum cardiomyopathy	Rhythm: PEA or VT/VF New heart failure symptoms POCUS: systolic dysfunction
Hypermagnesemia	Rhythm: PEA, bradycardia, prolonged PR, flattened P wave, prolonged QRS and QTc High magnesium level, weakness, decreased muscle tone/deep tendon reflexes, bradycardia or bradypnea POCUS: bradycardia
Ventricular fibrillation/ ventricular tachycardia	Rhythm: VT/VF/torsades de pointes Sudden cardiac death, cardiac disease, electrolyte abnormalities POCUS: fibrillation

Treatment

- Basic life support (BLS), advanced cardiac life support (ACLS).
- Peri-mortem cesarean section if no return of spontaneous circulation (ROSC) within 4 minutes.
- If hemorrhage: obstetric massive transfusion protocol (MTP).
- Maternal monitoring does not inform the clinician about the status of the fetus:
  - Time may not permit fetal heart rate monitor to be initiated.
  - Fetal oxygenation and acid–base status must be inferred.
- Resuscitate in supine position: manual left lateral displacement of the uterus.

Prognosis

- Maternal rates of survival to hospital discharge after cardiac arrest are as high as 60%.
- Maternal survival following peri-arrest cesarean section ranges from 35% to 55%.
- About 70% of fetal survivors of maternal cardiac arrest are delivered at 5 minutes; 95% within 15 minutes.

Post-partum hemorrhage

Background

Definition

- An estimated 500 mL of blood loss in a vaginal delivery.
- An estimated 1000 mL of blood loss in a cesarean section.
- Alternatively, any blood loss that causes hemodynamic instability in the mother.

Incidence/prevalence

- About 3% of pregnancies.
- About 650 deaths per year in the USA.

Etiology

• Uterine atony.	• Placenta previa.
• Retained products of conception.	• Invasive placentation.
• Birth trauma.	• Uterine rupture.

Predictive/risk factors

• Prior post-partum hemorrhage.	• Anemia.
• Age >40 years.	• Grand multiparity (≥5 births).
• High BMI.	• Hypertension.
• Multiple pregnancy.	• Prolonged placental delivery.
• Placenta previa.	• Instrumental delivery.

Diagnosis

- History: syncope, anemia, pregnancy complications, prior bleeding or family history of bleeding, prolonged delivery.

- Physical examination:
  - Primary survey: airway, ventilation, circulation, neurologic status.
  - Palpable abdomen: tenderness, peritonitis, palpable fetus.
  - Inspect vaginal introitus: birth trauma, ongoing bleeding.
  - Sterile speculum and bimanual exams: atony/retained products
- Investigations:
  - Kleihauer–Betke test: the KB test is the standard method of quantitating fetal–maternal hemorrhage (FMH). It allows calculation of the percentage of red blood cells in the mother's blood that are of fetal origin.
  - CBC, BMP, type and cross, coagulation panel, blood gas, Electrocardiogram.
  - FAST and cardiac ultrasound exam.

Treatment

- Centers should have a protocol for assessment and management of post-partum hemorrhage.
- Quantify blood loss.
- Monitor vital signs.
- Uterine atony is the most common cause of post-partum hemorrage:
  - Treat with uterotonic drugs, bimanual uterine compression, intrauterine balloon tamponade, uterine artery embolization.
- Traumatic lacerations need to be managed surgically.
- Retained placental tissue must be removed.
- Coagulopathy is treated with blood products and factor concentrates.
- Tranexamic acid is an antifibrinolytic drug that can reduce bleeding due to trauma or atony.
- Hysterectomy for patients with uterine rupture or diffuse placenta accreta.
- MTP for brisk bleeding, unstable patient.

Peri-partum cardiomyopathy

Background

Definition

- Heart failure in the last month of pregnancy or within 5 months post-partum, characterized by left ventricular systolic dysfunction without an alternative etiology.

Incidence/prevalence

The incidence varies by geographic region:

- USA: 1:1000–4000 live births.
- South Africa: 1:1000 live births; Haiti: 1:300 live births.

Etiology

- Myocardial insufficiency: proposed mechanisms include oxidative stress and prolactin upregulation.
- 16 kDa fragment of prolactin promotes apoptosis.
- Proposed insults: low selenium levels, viral, cytokines, hemodynamic stress.

Predictive/risk factors

- Multiparity.
- Maternal age >30 years.
- Pre-eclampsia.
- Prolonged tocolytics.
- Cocaine use.
- Black race/ethnicity.

Diagnosis

- Criteria:
  - Onset during the last month of pregnancy or 5 months post-partum.
  - LV systolic dysfunction (EF <45%).
  - No alternative cause identified.
  - No preceding cardiac disease.
- History: shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, fatigue, decreased exercise tolerance, bilateral lower extremity swelling.
- Physical examination: rales, S3 heart sound, bilateral lower extremity edema.
- Investigations: rule out alternative etiologies
  - CBC, BMP, troponin, BNP, TFTs.
  - Cardiac ultrasound.
  - Rarely cardiac MRI (gadolinium contraindicated ante-partum) or endomyocardial biopsy.

Differential diagnosis of peri-partum cardiomyopathy

Differential diagnosis	Features
Existing cardiac disease	Symptoms prior to pregnancy
Pulmonary embolism	History of VTE, sudden onset, unilateral lower extremity swelling
Viral myocarditis	Fever, viral illness

Treatment

Stable cases: outpatient management

- Prevent cardiac remodeling: angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) versus hydralazine and nitrate if ante-partum.
- Diuresis.
- Anticoagulation if EF <35%.

Unstable cases: inpatient management

- Treatment of pulmonary vascular congestion.
- Fetal cardiac monitoring: delivery if decompensation.
- Preload, afterload optimization.
- Vasopressors if needed to maintain SBP >90 mmHg:
  - Monitor for utero-fetal insufficiency.
- Inotropes and inodilators if needed for low cardiac output:
  - Consider monitoring urine output, serial cardiac US, placement of pulmonary artery catheter.

Agents for treating peri-partum cardiomyopathy

Focus of therapy	Medication regimen	Notes
Prevention of cardiac remodeling	Captopril 6.25–50 mg three times daily Ramipril 1.25–5mg twice daily Enalapril 1.25–0 twice daily Candesartan 2–32 mg daily Varsartan 40–160 mg twice daily Metoprolol tartrate .125–.25 mg daily Hydralazine 10–40 mg three times daily Nitroglycerin 10–20 ug/min then titrated to BP	ACEI and ARB contraindicated in ante-partum patients Beta-blockers should be continued up to 6 months after resolution

(*Continued*)

Focus of therapy	Medication regimen	Notes
Management of preload and pulmonary vascular congestion	Hydrochlorothiazide 12.5–50 mg daily Furosemide 20–80 mg once or twice daily Spironolactone 12.5–50 mg daily Norepinephrine 8–12 µg/kg/min	Institute in all hemodynamically stable patients
Inotropic support	Milrinone 0.125–0.5 µg/kg/min Dobutamine 2.5–10 µg/kg/min	Indicated for poor perfusion and SBP <90 mmHg
Prolactin inhibition	Bromocriptine 2.5 mg twice daily for 2 weeks, then 2.5 mg daily for 2 weeks	Requires concomitant anticoagulation due to thrombotic risk
Definitive end-stage therapy	Ventricular assist device Cardiac transplant	End-stage heart failure without recovery after 6 months

Prognosis

- Full recovery in 25–85% of cases.
- Progression to end-stage heart failure in 13–25% of cases.
- Mortality at 6 months: 3–30%.

Pulmonary embolic disease

Background

Definition

- Embolic occlusion of a pulmonary artery by venous thrombus or leaked fetal amniotic fluid that may result in hemodynamic changes due to mechanical obstruction, vasoconstriction, or inflammatory mediated myocardial depression.

Incidence/prevalence

- Venous thromboembolism (VTE) incidence: 5–12 events per 10 000 pregnancies ante-natally, 3–7 events per 10 000 pregnancies post-partum.
- VTE risk in pregnancy is increased 7–10× relative to the general population. The risk returns to baseline at 6 weeks post-partum.
- Amniotic fluid embolism (AFE) complicates 2–7 per 10 000 pregnancies

Etiology

- VTE: inhibition of fibrinolysis, venous stasis, endothelial activation.
- AFE: leakage of amniotic fluid into systemic circulation, resulting in endovascular dysfunction, mechanical obstruction, and myocardial depression.

Diagnosis

- VTE:
  - History: prior VTE, shortness of breath, chest pain, unilateral lower extremity erythema, edema, erythema. May present as sudden cardiac arrest.
  - Physical examination: tachypnea, unilateral lower extremity edema/erythema/tenderness.
  - Imaging: ECG or cardiac rhythm monitor, cardiac ultrasound, lower extremity venous ultrasound, CXR, CT angiogram (more diagnostic than V/Q scan).
- AFE:
  - History: intra-partum cardiac arrest. Alternatively sudden onset symptoms of heart failure.

- Physical examination: sudden loss of pulses. Rales, bilateral lower extremity edema.
- Imaging: POCUS TTE or TEE if available.

- Lab work, AFE and PE: blood gas, troponin, BNP, CBC, CMP, magnesium, INR, aPTT. D-dimer is not as useful in pregnant patients.

Treatment

- Cardiac arrest: follow ACLS guidelines.
- Shock: tPA 100 mg over 2 hours for PE; ECMO if rapidly available.
  - Optimize preload: crystalloid infusion, inotropic support.
  - Consider expedited caesarean section in unstable patients.
- VTE:
  - Stable patients: enoxaparin 1 mg/kg twice a day, dalteparin 200 U/kg each day or 100 U/kg twice a day, tinzaparin 175 U/kg each day. Titrate to factor Xa level: target range 0.5–1.1 U/mL.
  - Unstable patients or near delivery: heparin 80 U/kg bolus, infusion of heparin 18 U/kg, titrate to aPTT. Hold heparin 4 hours prior to delivery, resume 6 hours after vaginal delivery or 12 hours after cesarean.
- AFE: perfusion is rarely intact. Manage via BLS, ACLS, inotropic support, airway management.
  - Avoid excessive fluids.
  - After ROSC: immediate delivery in the case of viable fetus (>23 weeks).
  - If no ROSC: perimortem cesarean section at 4 minutes.
  - Evaluate for coagulopathy and treat if present.

Prognosis

- AFE: mortality is greater than 60%. Cardiac arrest survival <10%.
- PE: 15–18% mortality at 3 months.

Pre-eclampsia and eclampsia

Background

Definition

- Pre-eclampsia: new hypertension after >20 weeks of gestational age.
- Severe pre-eclampsia: pre-eclampsia with organ dysfunction.
- Eclampsia: seizure or acute neurological deficits in a patient with pre-eclampsia.

Incidence/prevalence

- Pre-eclampsia:
  - 2–8% of all pregnancies.
  - 25% progress to severe pre-eclampsia.
- Eclampsia: 1–3 per 1000 pregnant women.

Etiology

- Pre-eclampsia: endovascular dysfunction, possibly due to placental hypoxemia and inflammation. Can occur in the absence of placental abnormalities.
- Eclampsia: cerebral vasospasm, arterial insufficiency, local ischemia, disruption of the blood–brain barrier with cerebral edema.

Predictive/risk factors

- Pre-eclampsia: history of pre-eclampsia, primiparity, obesity, family history of pre-eclampsia, multiple pregnancies, history of hypertension or diabetes. Smoking decreases risk.

Diagnosis

- Pre-eclampsia: BP >140 mmHg on two separate readings more than 4 hours apart with either >300 mg urine protein/24 hours or protein : creatinine ratio ≥0.3.
- Severe pre-eclampsia: hypertension with proteinuria (as above) or organ system failure.
  - Vascular hypertension: BP >160 mmHg systolic or 110 mmHg diastolic on two readings more than 4 hours apart.
  - CNS: cerebral dysfunction or visual symptoms.
  - Hepatic: right upper quadrant pain or transaminases more than twice the upper limit of normal.
  - Hematologic: thrombocytopenia <100 000 platelets/μL.
  - Renal: serum creatinine >1.1 mg/dL or doubled above baseline.
  - Pulmonary: pulmonary edema.
- Eclampsia: Grand mal seizure after 20 weeks gestation with hypertension.

Treatment

- Pre-eclampsia:
  - Mild: control hypertension.
  - Severe: seizure prophylaxis, control hypertension, supportive care, delivery.
- Eclampsia: magnesium infusion, supportive care, delivery.

Table of treatment of severe pre-eclampsia

Focus of treatment	Intervention
Hypertension	Hydralazine: 5–20 mg IV every 30 minutes Labetalol: 10–20 mg IV every 10 minutes, double dose with re-dosing up to 80 mg per dose and total maximum of 220 mg
Seizure prophylaxis	First line: magnesium sulfate IV piggyback 4–6 g loading dose over 30 minutes with 2 g/h infusion. May load IM. Goal: serum magnesium level 4.8–8.4 mg/dL Continue through delivery Monitor for magnesium toxicity
Delivery	Definitive management for all viable fetuses Early viable gestations: may delay delivery for corticosteroid administration

Prevention/management of complications

- Monitor closely for magnesium toxicity.
- If patient suffers cardiac arrest while receiving magnesium, in addition to resuscitation, stop magnesium and treat toxicity empirically with calcium.

Prognosis

- Pre-eclampsia: 0.2% mortality with 5% risk of significant morbidity; 50 000–70 000 deaths worldwide annually.
- Eclampsia: 2–3 deaths per 10 000 live births in developed countries; 16 – 69 deaths per 10 000 live births in developing countries.

Reading list

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Papazian J, Kacmar RM. Obstetric hemorrhage: prevention, recognition, and treatment. Adv Anesth 2017;32(1):119–35.
Troiano NH, et al. AWHONN High-Risk and Critical Care Obstetrics, 3rd edition. Philadelphia: Wolters Kluwer Health, 2013.

Guidelines

National society guidelines

Title	Source	Date and reference
Cardiac Arrest in Pregnancy: A Scientific Statement from the AHA	American Heart Association	2015 Jeejeebhoy FM, et al. Circulation 2015;132(18):1747–73
Management of Pulmonary Embolism	American College of Cardiology	2016 Konstantinides SV, Barco S, Lankeit M, Meyer G. J Am Coll Cardiol 2016;67(8):976–90
Hypertension in Pregnancy	American College of Obstetricians and Gynecologists	2013 American College of Obstetricians and Gynecologists; Task Force on Hyptertension in Pregnancy. Obstet Gynecol 2013;122:1122–31
Amniotic Fluid Embolism: Diagnosis and Management	Society for Maternal-Fetal Medicine	2016 Society for Maternal-Fetal Medicine (SMFM) with the assistance of Pacheco LD, et al. Am J Obstet Gynecol 2016;215:B16–24

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

PART 6

Infectious Diseases

Section Editor: Janet M. Shapiro

CHAPTER 42

The Febrile Patient

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OVERALL BOTTOM LINE

- Fever in the ICU may be due to infectious and/or non-infectious causes.
- A judicious approach based upon detailed history and physical examination, existing risk factors, and local ICU infectious pathogens is required.
- In those with suspected sepsis or in whom clinical condition is deteriorating, empiric antibiotic therapy should be started as soon as possible.
- For most other patients, further diagnostic investigation with ongoing clinical assessment prior to the initiation of antibiotic therapy is reasonable.
- In an era of 'choosing wisely' to reduce unnecessary resource utilization, it is crucial to evaluate fever in the ICU in a rational and efficient manner.

Background

Definition of diseases

- The definition of fever depends on the purpose to which it is defined, the underlying disease, and the site of temperature measurement. Core body temperature is defined as the temperature of blood at the hypothalamus or within the core structures of the body.
- *Fever* in the ICU is usually defined as the elevation in body temperature to 38.3°C (101°F) or higher.
- Lower threshold may be used for the following patients: immunocompromised, elderly, burns, open surgical wounds, end-stage renal disease, end-stage liver disease, severe congestive heart failure, and those on hypothermic potentiating procedures such as continuous renal replacement therapy and extracorporeal membrane oxygenation.
- In neutropenic patients, fever is defined as a single oral temperature of 38.3°C (101°F) or a temperature elevation of 38°C (100.4°F) for 1 hour.
- *Fever equivalents*: significant proportions of infected patients are not febrile. Unexplained hypotension, tachycardia, tachypnea, confusion, rigors, oliguria, lactic acidosis, leukocytosis, or leukopenia with or without bands (of 10%) in the differential should also raise suspicion of sepsis.
- *Hyperthermia* is the term typically used for a non-infectious etiology-associated core body temperature of >40°C (104°F) (refer to pathophysiology above).
- *Hyperpyrexia* is the term typically used for an extraordinarily high fever (106.7°F and above), which can occur from an infectious etiology, but is more commonly due to a non-infectious etiology.

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Pathophysiology

- The hypothalamus is the 'thermostat' device of the human body and its 'normal set point' is around 37°C (98.6°F). Via the autonomic system, the hypothalamus continuously calibrates the body's core temperature to match its own set point.
- With an infection or a particular non-infectious process, elevated prostaglandin levels in the hypothalamus reset the 'thermostat' to a higher level. Activation of the sympathetic system results in conservation of heat loss (peripheral vasoconstriction) and increase in heat production (increase metabolism); the aim being to match the body's core temperature with that of the hypothalamic set point. Clinically, this stage manifests as shivering and cold extremities and the patient will often seek warm clothing.
- Reduction in the concentration of pyrogens and/or use of antipyretics will lead to relative downward resetting of the hypothalamic set point. Parasympathetic activation leads to peripheral vasodilation, in turn potentiating heat loss. Clinically, this stage manifests as sweating and warm extremities and patient seeking less clothing. This process continues until the body's core temperature matches the new 'lower' hypothalamic set point.
- Hyperthermia is not the same as 'fever' and it is not regulated at the level of the hypothalamus. In hyperthermia, body temperature increases in an uncontrolled fashion and surpasses its ability to lose heat. This process differs from fever as it is not hypothalamic mediated but there are no definitive clinical differentiating features. Temperature can increase to malignant levels and antipyretics do not work in such cases. External cooling is required to mitigate life-threatening temperature elevation. Examples include heat stroke, malignant hyperthermia, and neuroleptic malignant syndrome.

Incidence

Fever occurs in up to 70% of all ICU admissions. When due to an infectious cause, each case has the potential to progress to sepsis and septic shock.

Economic impact

- Fever in the ICU is associated with increased length of stay, cost of care, and antibiotic use.
- Poorer outcomes have been reported in patients with fever related to traumatic head injury, subarachnoid hemorrhage, and pancreatitis.
- Surgical incision site infections accounts for a considerable increased cost of ICU care.

Prevention

- Avoid the use of unnecessary indwelling catheters or devices that may result in infection and fever.
- Avoid the use of unnecessary medications that may cause fever.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Fever in an ICU patient should trigger a clinical assessment rather than automatic laboratory or radiologic testing for infection.
- The differential diagnosis for fever in an ICU patient is extensive.
- Clinical judgment based upon detailed history and physical examination, risk factors, and local ICU patterns can usually focus on the most probable causes.

Fever measurement

- Most guidelines consider intravascular thermistors and indwelling bladder catheter thermistors to be the most accurate and reliable methods to measure temperature; followed by rectal, oral, and tympanic membrane measurements.
- Axillary measurements, temporal artery estimates, and chemical dot thermometers are usually not recommended in ICU patients.
- Rectal thermometers should be avoided in neutropenic patients.

Differential diagnosis

Differential diagnosis based on the severity of fever (Table 42.1)

Although considerable overlap may exist, differential diagnosis can be approached based on four categories (infectious, non-infectious, mostly infectious, and mostly non-infectious). Incidence and prevalence of causes in each subgroup may vary based on existing risk factors and local ICU, hospital, and geographic patterns.

Table 42.1 Differential diagnosis based on the severity of fever.

38.3–38.8°C (101–101.8°F)		38.9–41°C (102–105.8°F)	≥41.1°C (106°F)
Infectious	**Non-infectious**	**Mostly infectious**	**Mostly non-Infectious**
Bacteremia (from any cause)	Benign postoperative fever	Abscess/empyema	Drug fever
Intravascular device infection	Alcohol/drug withdrawal	Necrotizing skin and soft tissue infections	Cerebral hemorrhage (especially pontine)
Surgical site infection	Pancreatitis	Septic arthritis	Acute febrile transfusion reactions
Ventilator-associated pneumonia	Febrile transfusion reactions	Cholangitis	Thyroid storm
Cellulitis	Drug fever	Sinusitis	Heat stroke
Urinary tract infection	Thyroid storm	Suppurative superficial thrombophlebitis	Malignant hyperthermia
Acalculous cholecystitis	Status epilepticus	Viremia	Neuroleptic malignant syndrome
Clostridium difficile colitis	Adrenal insufficiency	Neuroleptic malignant syndrome	
Meningitis/encephalitis	Neuroleptic malignant syndrome		
Endocarditis			

Differential diagnosis based on type of leukocytosis (Table 42.2)

Table 42.2 Differential diagnosis based on type of leukocytosis.

Neutrophilia or bandemia	Neutropenia	Eosinophilia	Basophilia
Most bacterial infections	Severe bacterial sepsis	Parasitic infections	Viral infections
	Viral infections	Fungal infections (e.g. allergic bronchopulmonary aspergillosis, coccidiomycosis)	Myeloproliferative disorders

(*Continued*)

Table 42.2 (*Continued*)

Neutrophilia or bandemia	Neutropenia	Eosinophilia	Basophilia
	Typhoid	Drug hypersensitivity reactions	Hypothyroidism
	Brucellosis	Hematologic and neoplastic disorders (e.g. graft versus host disease)	Hodgkin's lymphoma
	Rickettsia	Hypoadrenalism	Crohn's disease
	Tularemia	Atheroembolic disorders	Asthma
	Malaria	Sarcoidosis	
	Tuberculosis		
	Shigellosis		

Differential diagnosis of sources of fever with WBC count of >30 000/μL

- Pulmonary infections including empyema.
- *Clostridium difficile* colitis.
- Urinary tract infections.
- Vascular infections.
- Abscess.

Emergent causes of early postoperative fever (<48 hours)

- Myonecrosis (surgical wound infection).
- Pulmonary embolism.
- Alcohol withdrawal.
- Bowel leak.
- Adrenal insufficiency.
- Malignant hyperthermia.

Typical presentation

- Fever is usually noted during scheduled vital signs checks in the ICU or as part of the investigation for patients with suspected infection.
- Patients who are able to communicate in ICU may indicate having chills or rigors or this may be noted during ICU stay.

Clinical diagnosis

History and physical examination

- Vital signs.
- Vascular access, indwelling catheters, tubes.
- Skin – examine for rash, skin breakdown.
- Examine the surgical incision at least once daily for erythema, purulence, or tenderness.
- Examination of lungs, heart, abdomen.
- Examination of back and sacral area.
- Central nervous system examination including motor tone, nuchal rigidity.
- Observe appearance of urine, sputum, diarrhea.
- Muscle tenderness.

Common and important infectious causes of fever in the ICU

- *Intravascular devices*: a typical case would be abrupt onset of fever in a patient with a central venous catheter (non-tunneled or tunneled and >2 calendar days old) with signs of sepsis but no localized signs at the device site, and no evidence of other nosocomial infections. Difficulty drawing or infusing through

the catheter with peripheral blood cultures yielding organisms such as staphylococci, *Corynebacterium jeikeium*, *Bacillus* species, atypical mycobacteria, *Candida*, or *Malassezia* species strongly suggests infection of an intravascular device. A patient on hemodialysis via indwelling catheters may manifest signs of sepsis only when the catheter is used during dialysis.

- *Ventilator-associated events/pneumonia*: ventilator-associated events (VAEs) include a ventilator-associated condition (VAC), an infection-related ventilator-associated complication (IVAC), and ventilator-associated pneumonia (VAP), as defined by the Centers for Disease Control and Prevention (CDC). Each of these conditions requires deterioration in oxygen requirement after a period of stability. For more detailed information, refer to Chapter 44.
  - An increase of FiO_2 requirement of ≥20% or PEEP of ≥3 cmH_2O for a sustained period of ≥2 days is a VAC. The etiology could be infectious or non-infectious (e.g. pulmonary edema, atelectasis).
  - VAC in the setting of fever/hypothermia or WBC count >12 000 or <4000/μL and when a new antibiotic is added for a minimum of 4 days, is defined as an IVAC.
  - IVAC with additional evidence of infection, such as purulent secretions or positive respiratory cultures (irrespective of chest film findings), may represent probable or possible VAP.
- *C. difficile*: risk factors for the development of *C. difficile* infection include advanced age, critical illness, use of antibiotics and enteral tube feedings, and history of gastrointestinal surgery. Diarrhea (≥3 loose stools/24 hours) or ileus (postoperative patients tend to manifest as ileus rather than diarrhea) in such patients should be investigated for *C. difficile*. Elevated lactic acid with a daily up-trending WBC may be the only initial laboratory manifestations. WBC of >15 000/μL, serum albumin <3 g/dL, and/or a serum creatinine level ≥1.5 times the premorbid value are usually considered markers of severe disease and are more likely to be associated with ileus, pseudomembranous colitis, and toxic megacolon – a surgical emergency. The NAP1 strain is also a predictor of severe disease, poor outcome, and death.
- *Urinary catheter-associated bacteriuria or candiduria:* although counts of $>10^3$ cfu/mL represent true bacteriuria or candiduria in catheterized patients, there are no concrete data to show that higher counts are more likely to represent symptomatic infection than lower ones. In ICU patients, it usually represents colonization, and rarely causes fever or secondary bloodstream infection. Exceptions may apply to those with urinary tract obstruction, those with recent urologic procedure/surgery, or neutropenic patients. Catheter-associated urinary tract infection (CAUTI) may be caused by multiresistant nosocomial Gram-negative bacilli other than *Escherichia coli*, *Enterococcus* species, and yeasts.
- *Sinusitis*: nasotracheal intubation is the major risk factor for sinusitis, with a prevalence of up to 33% after 7 days of nasotracheal intubation. Most patients have fever without localized signs and symptoms.
- *Postoperative fever (beyond 48 hours after surgery)*: 25% of postoperative patients experience fever. Most fevers that develop after the first 48 hours of surgery should not be considered as benign (see later for benign postoperative fever). When evaluating postoperative fever, a helpful mnemonic is the 'four Ws': *wind* – pulmonary causes (pneumonia, aspiration, pulmonary embolism); *water* – UTI; *wound* – surgical site infection; *what did we do?* – iatrogenic causes (drug fever, transfusion reactions, intravascular device-related infection). Fever with signs of sepsis in patients beyond the first two postoperative days should trigger evaluation for anastomotic leak, bowel ischemia, and abscess.
- *Acalculous cholecystitis*: this most often occurs in critically ill patients and can be precipitated by a prolonged enteral fasting state, such as those on total parental nutrition. Other risk factors include trauma, surgery, burns, HIV infection, heart failure, and severe sepsis with multiple organ failure. Fever, leukocytosis, and vague abdominal discomfort may be the only clinical signs. The pathogenesis primarily involves bile stasis due to increased lithogenicity predisposing to gallbladder wall ischemia, necrosis, and resultant systemic inflammatory response. Secondary infection with *E. coli*, *Klebsiella*, *Enterococcus* species, and *Bacteroides* can occur. Diagnosis of acalculous cholecystitis is based on clinical suspicion plus imaging (ultrasound or CT scan). Treatment is usually with percutaneous cholecystostomy and antibiotics coverage.

- *Necrotizing skin and soft tissue infections*: this includes necrotizing fasciitis, myonecrosis, and gangrenous cellulitis. Causative organisms are usually group A β-hemolytic *Streptococcus* for necrotizing fasciitis, and anaerobes (*Clostridium perfringens*) in gangrenous cellulitis and myonecrosis. Polymicrobial infections are probably more common in each case. Typically, in necrotizing fasciitis the precipitating event is local trauma or severe muscle strain. On the other hand, myonecrosis usually results from either deep traumatic or surgical inoculation, or from hematogenous spread from an internal infectious focus in patient with underlying malignancy, neutrophil dysfunction, or bowel ischemia.
  - Irrespective of the precipitating event, the result is necrotizing soft tissue infection spreading along fascial planes and ultimately the overlying skin. Physical findings may be initially minimal (soft tissue edema and erythema) in the presence of severe pain and fever. Loss of pain is an ominous sign (ischemic peripheral neuropathy). The mortality rate is high without surgical intervention.
- *Surgical site infections*: apart from myonecrosis surgical site wound infections are generally rare in the first 3 days after surgery. Erythema, purulence, or wound tenderness are usually present. At-risk patients include those with diabetes, who are obese, or who had considerable contamination of the incision site during an emergent and prolonged procedure without prophylactic antibiotics (24 hours prior to surgery).
- *Central nervous system infection*: CNS infection as the cause of fever should be especially considered in those with intracranial devices. For example, an external ventricular drain carries a 10% risk of infection during the first 10 days. For more detailed information, refer to Chapter 47.

Common and important non-infectious causes of fever in the ICU

- *Benign postoperative fever* (within the first 48 hours after surgery): most fevers in the first two postoperative days are caused by the tissue injury and release of inflammatory cytokines. The temperature curve is generally highest on the first postoperative day and trends downwards toward normal by the fourth postoperative day. Careful history of the pre-surgical and intraoperative periods, and the physical examination, will prompt additional studies if needed.
- *Acute pancreatitis*: this is typically accompanied by abdominal pain, tenderness, distension, nausea and vomiting. Abdominal pain improves by leaning forward. Risks include alcoholism, gallstones, and hypertriglyceridemia (>500 mg/dL). There is no evidence to support empiric antibiotic coverage.
- *Pneumonitis*: such as in cases of aspiration pneumonia.
- *Mesenteric ischemia*: fever with severe abdominal pain with distention and tenderness (typically periumbilical pain is usually out of proportion to the physical exam findings), lactic acidosis, with or without hematochezia and ileus, in at-risk patients (those with severe atherosclerotic vascular disease of aorta) should raise suspicion of gut ischemia.
- *Drug-related fever*: fever due to drugs can present a diagnostic challenge since any drug can cause fever, which may manifest simply as fever alone or a life-threatening hypersensitivity reaction. There is nothing characteristic about drug fevers – it may occur days after administration and may take days to abate after discontinuation of the medication. Counter to general perception, rash occurs in only a small fraction of cases and eosinophilia is even rarer. The diagnosis of drug-induced fever is usually established on the basis of history, examination findings, and clinical course (temporal relationship of the fever to starting and stopping the drug).
  - Drugs can cause fever/hyperthermia via various mechanisms that may involve a single drug effect and/or a pharmacodynamic/pharmacokinetic interaction with other agents.
  - Common examples are listed where appropriate:
    - *By altering thermoregulation* – drugs such as butyrophenones (haloperidol), phenothiazines (prochlorperazine), antihistamines, and antiparkinson drugs.
    - *Hypersensitivity* – drugs such as antimicrobials (β-lactam drugs), anticonvulsants (phenytoin), antiarrhythmics (quinidine, procainamide), and antihypertensives (methyldopa).

  - *Malignant hyperthermia* – pathophysiology involves acute build-up of calcium in skeletal muscles in genetically susceptible patients resulting in muscular rigidity (often starts in chest wall and extremities), sympathetic nervous system overdrive, altered mental status, hypercapnia, and multiorgan failure. Succinylcholine and inhalation anesthetics (halothane) are the common precipitating agents. Although mostly seen during induction, presentation could be delayed for up to 10 hours.
- *Neuroleptic malignant syndrome*: pathophysiology involves central dopamine D2 receptor blockade leading to elevated temperature, muscular rigidity, altered mental status, and autonomic dysfunction usually within 4–14 days of either starting or increasing the dose of the offending agent(s). Multiorgan failure can occur in severe cases. Butyrophenones (haloperidol), antiemetic medication (prochlorperazine, metoclopramide), and withdrawal of antiparkinson medication are the common precipitating agents/factors in the ICU. Beside supportive care, management includes stopping thermogenesis with dantroline, and repleting dopamine with dopamine agonists (bromocriptine, amantadine).
- *Serotonin syndrome*: pathophysiology involves increased CNS serotonergic activity that leads to elevated temperature, altered mental status, neuromuscular hyperactivity (clonus, tremor, or hypertonia), and autonomic dysfunction, usually within 24 hours of either starting or increasing the dose of an offending agent(s). Therefore any medication with serotomimetic or serotonergic properties when used alone or in combination can precipitate serotonin syndrome. Examples include: antidepressants (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs)), antibiotics (linezolid), opioid analgesics (fentanyl), and even antiemetics (metachlopramide, ondansetron).
- *Substance abuse*: synthetic cannabinoids (e.g. synthetic marijuana, K2, Spice), synthetic cathinones (bath salts), amphetamine, cocaine, LSD, and MDMA.
- *Drug withdrawal*: fever can occur with severe alcohol withdrawal but usually is not associated with opioid or benzodiazepine withdrawal.
- *Febrile transfusion reactions*: a fever elevation of >1.1°C (>2°F) during transfusion needs to be assessed and evaluated carefully. If transfusion reaction is suspected, assume it to be hemolytic until proven otherwise (via laboratory investigations).
- *Febrile non-hemolytic transfusion reaction*: although the overall incidence has decreased, this remains the most common transfusion reaction, occurring during or up to 4 hours after red blood cell (RBC) or platelet transfusion. Pathophysiology involves either preformed donor cytokines or recipient anti-HLA antibody-mediated donor WBC destruction.
  - *Transfusion-related acute lung injury (TRALI)*: this rare transfusion reaction is the leading cause of transfusion-related deaths in the USA. Clinically, it presents as acute respiratory distress occurring within 6 hours of transfusion. Lack of pre-existing acute lung injury and other risk factors for pulmonary edema are two additional diagnostic criteria. Fever, chills, and transient hypertension followed by shock is the typical course. Pathophysiology is not well understood. Platelet and plasma rather than RBS transfusions are most often associated with TRALI.
  - *Acute hemolytic transfusion reaction*: intravascular hemolysis due to ABO incompatibility presents as chills, fever, back/flank pain, hemoglobinuria, bleeding, disseminated intravascular coagulation, and even multiorgan failure.
  - *Delayed hemolytic transfusion reactions*: hemolysis occurring at least 24 hours but less than 28 days after transfusion. Antibody is formed (either primarily or from an anamnestic response) to non-ABO red cell antigen leading to extravascular hemolysis. Presentation is usually asymptomatic hemolytic anemia, but fever can occur. A peripheral blood smear usually shows spherocytes and a Coombs test is positive.
  - *Transfusion-transmitted infection*: this is extremely rare. Platelet contamination with Gram-positive cocci is the commonest followed by red cells contaminated with Gram-negative rods (*Yersinia enterocolitica* is the most reported historically). Signs and symptoms will mimic sepsis.

Transfusion reactions (Table 42.3)

Table 42.3 Febrile and afebrile tranfusion reactions.

Febrile		Afebrile	
Acute	**Delayed (>24 hours)**	**Acute**	**Delayed (>24 hours)**
Febrile non-hemolytic	Delayed hemolytic	Allergic	Delayed serologic
Transfusion-related acute lung injury	Transfusion-associated graft versus host disease	Hypotensive	Post-transfusion purpura
Transfusion-transmitted infection		Transfusion-associated dyspnea	
Acute hemolytic		Transfusion-associated circulatory overload	

Examples in each group are arranged in decreasing order of frequency. Overall, febrile non-hemolytic and afebrile allergic are the most common transfusion reactions. TRALI > TACO > acute hemolytic are, however, the leading causes of transfusion-related deaths in the USA.

Less common non-infectious causes of fever in the ICU

- Status epilepticus.
- Pulmonary embolism.
- Gout: the knee is the commonest site. Keep a high index of suspicion in those with a prior history of gout.
- Stroke.
- Myocardial infarction (MI).
- Thyroid storm.
- Transplant rejection.
- Tumor lysis syndrome: typically in the setting of lymphomas with a high tumor burden.
- Dressler's syndrome (pericardial injury syndrome): pericarditis with or without a pericardial effusion typically 7 days post MI constitutes post-cardiac injury syndrome.

Questionable causes of fever in the ICU

- Atelectasis.
- Deep venous thrombosis.

Laboratory diagnosis

In most patients, a thorough review of the medical history (including travel history) and physical examination will help in determining the cause of fever. Routine 'knee jerk' battery testing should be discouraged.

List of diagnostic tests

- *Routine blood tests*: to start with, each patient should have a baseline comprehensive metabolic panel (including liver function tests), complete blood count with differential and basic coagulation profile. In addition, thyroid function tests, disseminated intravascular coagulation profile, and serum cortisol if deemed necessary. Such a battery of basic investigations is cost effective and almost always helps in narrowing the differential diagnosis.

- *Blood cultures*: paired aerobic and anaerobic blood cultures (at least one culture set from a peripheral vein), are collected in a sterile manner prior to the initiation of antibiotics. Skin preparation should be performed utilizing chlorhexidine. Quantitative catheter tip cultures have been utilized for diagnosis of CLABSI, using growth of >15 cfu as positive. A positive catheter tip culture itself, however, is not sufficient for diagnosis. Blood cultures should be drawn only if there is clinical suspicion of continuing or recurrent bacteremia or fungemia or for test of cure 48–96 hours after initiation of appropriate therapy for bacteremia/fungemia. Immunocompromised patients may warrant culture of blood for unusual pathogens.
- *Respiratory specimen*: for Gram stain and culture if suspecting a lower respiratory tract infection. Respiratory specimens can be obtained via expectoration, induction, tracheal aspiration, or bronchoalveolar lavage (BAL). Bronchoscopy should be performed for diagnosis of *Pneumocystis jirovecii*, *Aspergillus* and other filamentous fungi, *Nocardia*, *Legionella*, and *Mycobacterium* species. Not all organisms that are recovered from respiratory secretions are pathogenic. Enterococci, viridans streptococci, coagulase-negative staphylococci, and *Candida* species are unlikely to be respiratory pathogens. Isolation of cytomegalovirus (CMV) is common from BAL of HIV patients (especially those with *Pneumocystis* pneumonia) and has even been associated with poorer prognosis, but CMV in itself is usually a bystander rather than a pathogen in such cases. See Chapter 46 for further information on pneumonia.
- *Pleural fluid*: many febrile patients in an ICU have small amounts of pleural fluid and it is not necessary to perform a diagnostic thoracentesis in every febrile patient. However, patients with a significant parapneumonic effusion should undergo thoracentesis if fluid is accessible.
- *Stool*: if suspecting *C. difficile*, polymerase chain reaction (PCR) assays are rapid and very sensitive methods to confirm the presence of *C. difficile* toxin. Unless the patient was admitted with diarrhea, is infected with HIV, or is a part of an outbreak evaluation, stool for bacterial cultures or ova and parasite examination is usually not required.
- *Urine for urinalysis and culture*: this should be done in all patients who present with an indwelling urinary catheter with a suspected UTI. Routine monitoring or 'surveillance' cultures of urine contribute little to management of a febrile patient. Of note, in contrast to community-acquired UTI, rapid dipstick tests alone are unreliable to detect CAUTI. The rapid dipstick test relies upon leukocyte esterase (corresponds to pyuria) and nitrites (corresponds to Enterobacteriaceae), both of which may not be present in CAUTI due to *Enterococcus* species, *Candida* species, and coagulase-positive *Staphylococcus* species.
- *Wound culture*: if suspecting surgical site (wound) infection, the wound should be opened, drained, and then cultured. Superficial cultures are of limited value.
- *Lactic acid*: it is recommended that serum lactate be drawn if infection is suspected in order to assess the severity of sepsis. Serum lactate levels should not be used as a sole resuscitation endpoint. Rather, lactate should be used as one of the hemodynamic parameters, in addition to urine output and organ perfusion examination. Irrespective of the primary cause of lactic acidosis, if levels continue to rise (or not improve) despite adequate therapy, one may consider bowel or limb ischemia as a possible cause. Patients with baseline thiamine deficiency may exhibit delayed clearing of lactic acid.
- *Procalcitonin*: emerging data suggest it is a potentially useful biomarker for generalized bacterial infection with a good negative predictive value. Downtrending levels may help in guiding the duration of antibiotic therapy. The reference value in adults is ≤0.15 ng/mL and an elevated level (>2 ng/mL) is usually associated with severe bacterial infections. However, levels may not rise with localized infections (such as osteomyelitis or abscess). Furthermore, patients with major burns, severe trauma, acute multiorgan failure, or major abdominal or cardiothoracic surgery can also have elevated levels. Viral infections and chronic inflammatory states are associated with normal levels. Therefore, procalcitonin is not a definitive biomarker, but rather can be used in the clinical context.

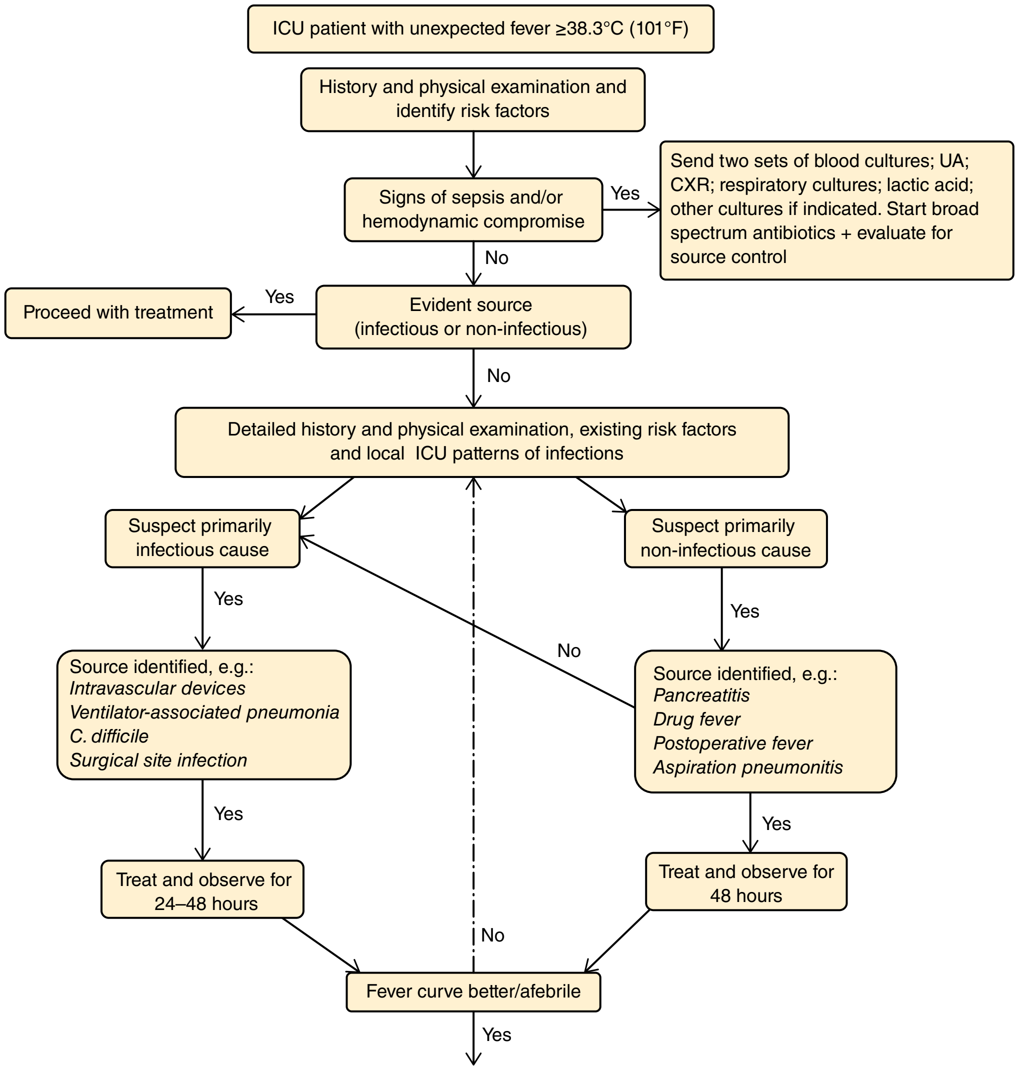
- *Antigen testing*:
  - Urinary antigen for *Legionella pneumophila* type 1 and *Streptococcus pneumoniae*.
  - Blood antigen for CMV, histoplasmosis, and cryptococcosis.
  - Serum or body fluid PCR for CMV, varicella-zoster virus, human herpes virus 6, and adenovirus.
  - Cerebrospinal fluid (CSF) molecular testing in those with suspected encephalitis. Panel should include adenovirus, enterovirus, herpes simplex virus (HSV) 1 and 2, varicella-zoster virus, CMV, Epstein–Barr virus, and human herpesvirus 6. From June through November, in the USA, the panel should also include West Nile virus, St. Louis encephalitis, Eastern equine encephalitis, Cache Valley, and California serogroup viruses. When sending CSF for PCR viral studies, the sample should be withdrawn from the least bloody tube because blood is an inhibitor of PCR reaction (false negative results). Of note, PCR can be falsely negative within the first 72 hours of onset of HSV encephalitis. A repeat CSF PCR in such cases will yield positive results.
  - Blood galactomannan and β-D-glucan for aspergillosis and *Candida*. The high negative predictive value makes these tests useful to exclude invasive fungal infection. Serial levels can be obtained to assess response to treatment.
- *Lumbar puncture* (LP): if altered consciousness is unexplained in the setting of fever, a diagnostic LP should be considered unless there is a contraindication. If new focal neurologic findings suggest disease above the foramen magnum, an imaging study should be performed prior to performing an LP. Opening pressure should always be measured. Routine LP results in meningoencephalitis/encephalitis and cases of early meningitis can be misleading and should never be used alone to refute a diagnosis.

List of imaging techniques

- *CXR*: although sensitivity and specificity is low for an AP portable CXR, among all radiographic signs unilateral air bronchograms have been shown to have the best predictive value for pneumonia.
- *CT scan*: CT chest is useful in immunocompromised patients with unrevealing CXR but suspected to have small nodular or cavitary pulmonary lesions. Abdominal CT is useful in those with suspected intra-abdominal pathology (e.g. abscess, pyelonephritis, pancreatitis, vascular graft infection, intestinal obstruction and colitis).
- *Ultrasound*: perform a renal US if suspecting pyelonephritis or hydronephrosis, or a right upper quadrant US if suspecting acute cholecystitis, in which it has a sensitivity of 91% and a specificity of 79%. If US is equivocal, a HIDA scan can be utilized.
- *Hepatobiliary iminodiacetic acid (HIDA) scan*: in a normal (or negative) HIDA scan, the gallbladder is visualized (hence cystic duct is patent), whereas lack of gallbladder visualization (within 4 hours of IV contrast) constitutes a positive study and indicates the presence of cholecystitis or cystic duct obstruction. For acute calculus cholecystitis, HIDA is 97% sensitive and 90% specific, whereas it has both poor negative and positive predictive power in acalculous cholecystitis.
- *WBC tagged scan*: in those with an occult source of infection.
- *Transthoracic echocardiogram (TTE)*: as part of initial evaluation for endocarditis.
- *Transesophageal echocardiogram (TEE)*: for bacterial endocarditis.
- *Electroencephalogram (EEG)*: for status epilepticus.

Diagnostic algorithm (Algorithm 42.1)

Algorithm 42.1 Determination of the cause of fever in the ICU



Treatment

- There is no role for routine pharmacologic treatment of fever with antipyretics or external cooling. Some evidence suggests that the use of antipyretics may worsen outcomes in sepsis. Exceptions to this are when the fever may be detrimental to the outcome (e.g. ischemic brain injury or increased intracranial pressure) or temperature >41°C (≥105.8°F).
- Treat the underlying cause of fever based on current guidelines.
- Those who appear sick or in whom the clinical condition is deteriorating (in shock) empiric antibiotic therapy should be started as soon as possible. For most other patients, further diagnostic investigation with ongoing clinical assessment prior to the initiation of antibiotic therapy is reasonable.
- Narrow antibiotic coverage as soon as possible based on clinical judgment and culture results.

- Prompt expert consultation when deemed necessary, such as surgical consultation for severe *C. difficile* colitis and necrotizing fasciitis. Infectious disease consultation should be sought for immunocompromised patients.
- For immunocompromised patients, the general rule is to be aggressive in pursuing a specific microbiologic diagnosis, and invasive diagnostic techniques are often required.
- Fever of neurologic origin is a diagnosis of exclusion but an independent predictor of poor outcome, especially in patients with intracerebral hemorrhage. In patients with neurologic injury and infectious or non-infectious source of fever, fever in excess of 38.3°C (101°F) should be treated to achieve therapeutic normothermia. Those refractory to acetaminophen and without an infectious cause may require cooling devices. Adhesive surface cooling systems (and even endovascular heat exchange catheters) are better at maintaining normothermia than conventional treatment.
- Post-cardiac arrest patients with fever and who are not considered candidates for therapeutic hypothermia should be actively treated in order to achieve and maintain therapeutic normothermia.
- In general for an ICU fever, NSAIDs should be avoided given their propensity to cause acute kidney injury.

CLINICAL PEARLS

- Unless indicated for neurologic injured patients, avoid routine pharmacologic treatment of fever.
- For those whose clinical condition is deteriorating, empiric antibiotic therapy should be started as soon as possible.
- For immunocompromised patients, be aggressive in pursuing a specific microbiologic diagnosis.

Special populations

Immunocompromised patients

Early diagnosis and specific therapy of opportunistic infections is the cornerstone of successful treatment in the following group of patients:

- *Neutropenic patients*: neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/μL or an ANC that is expected to decrease to <500 cells/μL during the next 48 hours. A single oral temperature of 38.3°C (101°F) or a temperature elevation of 38°C (100.4°F) for 1 hour is considered as fever. In two-thirds of the cases, the initial evaluation may not identify a focus of infection. This may be in part due to prior antibiotic use. Patients with an anticipated prolonged (>1 week) ANC count of <100 cells/μL following cytotoxic chemotherapy as well as those with hypotension, pneumonia, new-onset abdominal pain, or neurologic changes should be considered as high risk patients.
- *Asplenic patients*: overwhelming sepsis caused by the encapsulated bacteria *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides* is of particular concern. Adults who do not have antibodies to these organisms succumb to sepsis at 58 times the rate of the general population. Although increased risk persists throughout life, most infections occur within the first 2 years after splenectomy.
- *Other immunocompromised patients*: those on corticosteroids, biologic T lymphocyte-depleting agents or drug-induced T-cell depression, HIV/AIDS, and transplant patients should all be considered immunocompromised. Fever in such non-neutropenic immunocompromised patients is more often caused by infection at specific sites (e.g. *Pneumocystis jirovecii* in HIV-infected patients), but a specific site is often not clinically defined initially. In patients receiving allogeneic bone marrow transplants, consider interstitial pneumonitis, especially due to CMV, from 30 to 60 days after transplantation. Although CMV is also important in patients receiving solid organ transplants, it is relatively uncommon in patients receiving autologous bone marrow transplants.

Reading list

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Suggested websites

http://www.cdc.gov/nhsn/acute-care-hospital/vae

www.mhaus.org

www.nmsis.org

Guidelines

National society guidelines

Title	Source	Date and reference
Guidelines for Evaluation of New Fever in Critically Ill Adult Patients: 2008 Update from the American College of Critical Care Medicine and the Infectious Diseases Society of America	American College of Critical Care Medicine and the Infectious Diseases Society of America	2008 Crit Care Med 2008;36(4):1330–49
Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients With Cancer: 2010 Update by the Infectious Diseases Society of America	Infectious Diseases Society of America	2011 Clin Infect Dis 2011;52(4):427–31

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

with website

CHAPTER 43

Sepsis

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OVERALL BOTTOM LINE

- Sepsis is an inflammatory host response to infection and is a clinical syndrome that can progress to organ failure and shock.
- Sepsis is a leading cause of mortality and critical illness worldwide. Mortality increases with disease severity.
- It can affect any group of patients but is most severe in the elderly and immunocompromised.
- Early sepsis identification and aggressive resuscitation with intravenous fluids and broad spectrum antibiotics are key to improving clinical outcomes.
- Sepsis is difficult to define. There is no gold standard diagnostic test for sepsis. Definitions and disease classifications are continuously evolving and may change in the future.

Background

Definition

- In 2016 a new consensus definition of sepsis was published by the Society of Critical Care Medicine. However, the acceptance of these criteria and their impact are not yet established. There is ongoing debate regarding the specific definition and disease classifications of sepsis.
- Sepsis is an inflammatory host response to infection that can lead to life-threatening organ dysfunction.
- Major international organizations differ in their definition and classification system of sepsis (Table 43.1).

Incidence/prevalence

- In the USA there are approximately 970 000 sepsis cases per year.
- The incidence rose almost 9% annually during the past two decades.
- Sepsis mortality overall is greater than 50% and increases linearly with severity of disease, ranging from 10% to 80%.

Economic impact

- Accounts for 40% of ICU expenditures.
- Average length of stay is 75% higher than most other conditions, increasing with disease severity.
- Cost per hospitalization also increases with disease severity, from $16 000 to $38 000 in the USA.
- USA annual cost was $24 billion in 2013, 13% of total hospital costs, but accounting for only 3.6% of hospital admissions.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Table 43.1 Definitions of sepsis.

Organization	Key parts of definition
SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference, 2001	*Sepsis*: clinical syndrome defined by both the presence of infection and more than one of the systemic inflammatory response syndrome (SIRS) criteria: • Temperature >38°C or <36°C • Heart rate >90 bpm • Respiratory rate >20 breaths/min or a $PaCO_2$ of <32 mmHg • WBC >12 000 or <4000 mg/dL *Severe sepsis*: sepsis complicated with end-organ dysfunction. (See also Table 1 in the original paper for a list of non-specific physical, hemodynamic, and laboratory variables consistent with sepsis) *Septic shock*: state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes *Hypotension*: systolic arterial pressure below 90 mmHg, a MAP <60, or a reduction in SBP of >40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension
Surviving Sepsis Campaign (used by the National Quality Forum (NQF) and Centers for Medicare and Medicaid Services (CMS))	*Sepsis*: suspected infection in the setting of two or more of the SIRS criteria: • Temperature >38.3°C or <36°C • Heart rate >90 bpm • Respiratory rate >20 breaths/min or a $PaCO_2$ of <32 mmHg • WBC >12 000 or <4000 mg/dL; >10% bands *Severe sepsis*: defined as sepsis with markers of end-organ dysfunction, or lactic acidosis above upper limit laboratory normal (usually >2 mmol/L) *Septic shock*: a lactic acidosis >4 at any time, or fluid-resistant hypotension
SCCM/ESICM Task Force, 2016	Consensus definition published in 2016, not yet endorsed by all medical societies and has not yet been incorporated into sepsis treatment protocols SIRS has been removed as part of the definition, and terminology such as severe sepsis, sepsis syndrome, and septicemia have been eliminated *Sepsis*: life-threatening organ dysfunction caused by a dysregulated host response to infection. Outside the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified using the quick sequential organ failure assessment (qSOFA) score (SBP <100 mmHg, respiratory rate >22 breaths/min, altered mental status) In the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified by the presence of 2 or more SOFA points or a change in SOFA score by 2 or more points from baseline *Septic shock*: subset of sepsis in which profound circulatory, metabolic, and cellular abnormalities are associated with a greater risk of mortality than sepsis alone. Adult patients with septic shock can be identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean BP ≥65 mmHg and having a serum lactate >2 mmol/L after adequate fluid resuscitation

Etiology

- Sepsis can occur as a result of both community-acquired and healthcare–associated infection of any source and type (fungal, bacterial, viral).
- Pneumonia is the most common cause, accounting for about half of all cases, followed by intra-abdominal and urinary tract infections.
- Blood cultures are typically positive in only one-third of cases.

Pathology/pathogenesis

- The pathogenic mechanisms underlying sepsis and septic shock are complex.
- Microorganisms at the port of infection enter the bloodstream. In response, a large number of host pro- and anti-inflammatory mediators are released from cells (endothelial cells, monocyte macrophages, neutrophils) and plasma proteins (coagulation, fibrinolytic, and complement systems). These host-released mediators have major physiologic effects on multiple organ systems.
- The balance between the pro- and anti-inflammatory response will determine the degree of organ damage or infection proliferation.
- The direction, extent, and duration of these reactions are determined by both host (genetic characteristics, age, coexisting illnesses, medications) and pathogen (microbial load and virulence) factors.
- Septic shock can cause dysregulation in the cardiovascular, respiratory, renal, metabolic, hematologic, hepatic, and nervous systems.
- Severe sepsis is frequently associated with altered coagulation in some cases leading to disseminated intravascular coagulation (DIC).

Predictive/risk factors

- Immunosuppression.
- Age >65 years.
- Diabetes.
- Cancer.
- Previous hospitalizations.
- Genetic factors.
- Chronic lung disease.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Reduce the use of unnecessary invasive procedures, indwelling catheters, and devices.
- Avoid prolonged use of any indwelling devices (e.g. Foley catheters, peripheral and central lines).
- Give timely and age-specific vaccinations.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- There is no gold standard diagnostic test for sepsis.
- Sepsis has many clinical presentations, including malaise and weakness, focal symptoms of infection, altered mental status, and distributive shock.
- Serum lactate should be ordered for any patient with suspected sepsis, along with other diagnostic studies.

Differential diagnosis

Differential diagnosis	Features
Alcohol withdrawal	Tremulousness, hypertension, tongue fasciculation, restlessness, seizures, history of alcohol abuse
Influenza	High grade fevers, rigors, cough, tachycardia, variable presentation from well appearing to toxic
Unspecified gastroenteritis	Vomiting and diarrhea, nausea, abdominal discomfort without focal pain or tenderness, afebrile or low grade temperature, otherwise well appearing
Hypovolemia/dehydration	Hypotension, tachycardia, afebrile, dry mucous membranes, poor skin turgor, slow capillary refill
Upper gastrointestinal bleeding	Hypotension, weakness, tachycardia, lactic acidosis, melena, hematemesis
Lower gastrointestinal bleeding	Hematochezia, hypotension, weakness, tachycardia, lactic acidosis
Pancreatitis	Abdominal pain, leukocytosis, lactic acidosis, hypovolemia, hypotension

Typical presentation

- Presentation varies widely depending on the etiology and severity of sepsis, patient comorbidities, and duration of illness.
- Typical symptoms include fever, chills, diaphoresis, malaise, and weakness.
- Source-specific symptoms may also be present (Table 43.2).
- Immunocompromised and elderly patients may present with more subtle or atypical features (see Special populations section).

Table 43.2 Source-specific symptoms and signs of sepsis.

Source/system	Classic symptoms	Classic signs
Central nervous system (meningitis, encephalitis)	Headache, neck pain, neck stiffness, confusion, seizures	Disorientation, loss of consciousness, myoclonus, nuchal rigidity, focal neurologic deficit
Respiratory system (pneumonia, empyema)	Shortness of breath, cough, chest pain	Tachypnea, nasal flaring, tripoding, hypoxia, focal diminished breath sounds, rales
Gastrointestinal/hepatobiliary (cholecystitis, cholangitis, colitis, appendicitis)	Pain, vomiting, diarrhea	Focal abdominal tenderness, rebound tenderness, local or diffuse guarding, abdominal rigidity
Urinary tract	Pain with urination, back pain, flank pain	Suprapubic tenderness, costovertebral angle tenderness
Heart (myocarditis, endocarditis)	Dyspnea, chest pain, pleuritic pain	Hypotension, tachycardia, dysrhythmias, cool extremities
Skin/soft tissue (cellulitis, abscess, fasciitis)	Rash, localized pain	Focal warmth, induration, fluctuance, crepitations, pain out of proportion to exam findings

Clinical diagnosis

History

- Duration and progression of symptoms.
- Recent travel.
- Known sick contacts.
- Recent antibiotic use.
- History of infections.
- Recent hospitalizations or surgeries.
- Change in urine output.
- Evidence of immunosuppression.
- Chronic disease states.

Physical examination

- Assess the presence of any of the SIRS criteria (see Table 43.1).
  - One in eight cases of sepsis have been found to be SIRS negative.
- Hypotension (MAP <65) or capillary refill >2 seconds may be markers of poor end-organ perfusion, although absence of these findings does not exclude it.
- Examine any foreign bodies (indwelling catheters, implanted medical devices) for warmth, induration, tenderness, or purulent drainage.
- Focus the physical exam based on the kind of infection(s) suspected (Table 43.2) such as pneumonia, urinary tract infection (UTI), cellulitis, central nervous system or intra-abdominal infection, or infection of foreign bodies.

Useful clinical decision rules and calculators

- In the 2016 SCCM/ESICM sepsis definition (see Table 43.1) the sequential organ failure assessment (SOFA) score is used to identify patients at higher risk of dying from sepsis. The applicability of this definition will require future prospective validation.
- The SOFA score is an illness severity score which is mainly used to predict the mortality of critically ill patients. It is helpful in assessing the severity of end-organ damage in sepsis, using clinical parameters to predict mortality risk.
  - In the ICU, patients with suspected infection who are likely to have poor outcomes can be identified by the presence of 2 or more SOFA points or a change in SOFA score by 2 or more points from baseline (Table 43.3).
  - Outside the ICU, these patients can be identified using the qSOFA score (any two of three elements: SBP <100 mmHg, RR >22 breaths/min, altered mental status).

Disease severity classification

- According to the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference, sepsis is classified as the presence of SIRS criteria with a source of infection.
- Severe sepsis is classified as evidence of end-organ dysfunction in the setting of infection (see next section for parameters of end-organ dysfunction).
- Septic shock is classified as sepsis-induced hypotension that is refractory to appropriate fluid bolus.

Laboratory diagnosis

List of diagnostic tests

- All patients suspected of sepsis should receive: CBC, basic metabolic panel, at least two sets of blood cultures, CXR, and serum lactate.

Table 43.3 SOFA scoring system.

Organ System	Score				
	0	1	2	3	4
Respiratory: PaO_2 kPa/ FiO_2 mmHg	>400	≤400	≤300	≤200	≤100
Renal: creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9; urine output <500 mL/day	>5; urine output <200mL/day
Hepatic: bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12
Cardiovascular: hypotension	No hypotension	MAP < 70mmHg	Dopamine <5[a], dobutamine (any dose)	Dopamine >5[a] or epinephrine ≤ 0.1[a] or norepinephrine 0.1[a]	Dopamine >5[a] or epinephrine ≤ 0.1[a] or norepinephrine 0.1[a]
Hematologic: platelet count (1×10^3)	>150	≤150	≤100	≤50	≤20
Neurologic: GCS score	15	13–14	10–12	6–9	<6

[a]Adrenergic agents administered for more than 1 hour (doses in µg/kg/min).

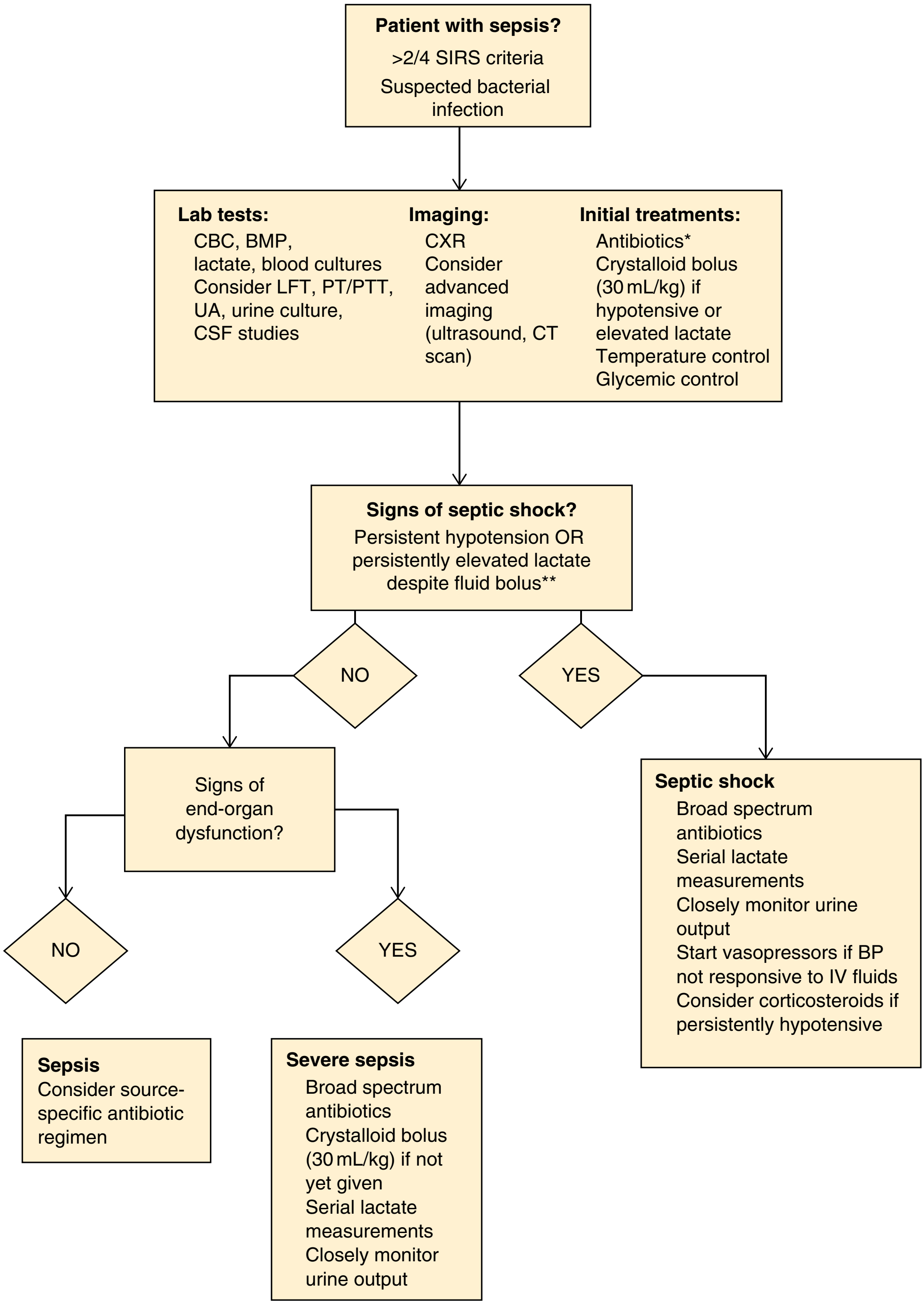
  - Cultures should be drawn prior to initiation of antibiotics unless it would lead to a significant (>45 minutes) delay to antibiotic administration.
- Coagulation testing (PTT, PT/INR) and hepatic function tests may be necessary if severe sepsis or septic shock is suspected.
- CXR if the lungs are a suspected source of infection.
- Patients may have a leukocytosis, leukopenia, or bandemia. They may also demonstrate signs of end-organ damage such as hypoxemia, acute oliguria, elevated creatinine (>2 mg/dL) or bilirubin (>2 mg/dL), thrombocytopenia (platelets <100 000/µL), or coagulopathy (INR >1.7 or PTT >60sec).
- Urinalysis and urine cultures should be sent if there is strong suspicion for urinary infection.
- Lumbar puncture, thoracentesis, paracentesis, and wound culture may be indicated depending on clinical scenario and suspected source of sepsis.

List of imaging techniques

- CXR for patients with signs or symptoms of respiratory dysfunction.
- Advanced imaging may be warranted depending on the suspected source: e.g. CT scan for intra-abdominal, intracranial, or deep tissue infections; MRI for suspected spinal epidural abscess.
- Bedside point-of-care ultrasound to assess volume status and fluid responsiveness.

Diagnostic and management algorithm (Algorithm 43.1)

Algorithm 43.1 Diagnosis and management of sepsis and septic shock



*Consider starting antibiotics if strong suspicion for a specific source.
**The CMS definition of septic shock includes any sepsis-associated lactate >4 mmol/L

Potential pitfalls/common errors made regarding diagnosis of sepsis

- Failure to consider sepsis, thereby delaying identification and treatment.
- Failure to obtain serum lactate to identify 'occult' sepsis or stratify severity of sepsis.
- Failure in obtaining cultures of blood, urine, or other potential sources of sepsis prior to initiating antibiotic therapy.
- Being falsely reassured by patient's clinical appearance, vital signs, or low serum lactate.
- Ruling out a source of infection based on poorly sensitive physical exam findings, e.g. normal lung exam, minimal abdominal tenderness, well-appearing patient.

Treatment

Treatment rationale

- Cornerstones of treatment include fluid resuscitation, controlling the source of infection, administration of antimicrobials, and supporting vital signs and end-organ function.
- Antimicrobials:
  - Time to antimicrobials is a critical determinant of survival in severe sepsis/septic shock.
  - If sepsis is strongly suspected, empiric broad spectrum antibiotics should be started without waiting for confirmation by imaging or lab analysis. If the patient is found to be in severe sepsis or septic shock, antibiotics should be administered ideally within 1 hour of sepsis presentation.
  - If the patient is in good health at baseline, well appearing, with a reassuring serum lactate and a confirmed source of infection, a more targeted antimicrobial regimen may be considered.
- Source control:
  - Remove any indwelling catheters or medical devices if suspected to be a source of infection.
  - Emergent subspecialty consultation is crucial when solid-organ infection is suspected (appendicitis, cholecystitis, endometritis, abscesses).
- Fluid resuscitation:
  - Fluid bolus of 30 mL/kg.
  - Goal is a mean arterial pressure >65 mmHg.
  - In the setting of lactic acidosis, trend serum lactate until it reaches normal limits.

Supportive care measures

Hypotension	Fluid administration as mentioned earlier Start vasopressors if patient deemed poor candidate for further fluid boluses Initial vasopressor of choice: norepinephrine 0.1–3 μg/kg/min, titrate to goal MAP Second choice: add epinephrine as second agent, dobutamine (in the setting of myocardial dysfunction), phenylephrine (in hyperdynamic shock), or vasopressin (0.02–0.04 U/min) Consider corticosteroids (hydrocortisone 100 mg IV) if hypotension is refractory to fluids and vasopressors
Tachycardia	Identify cause (fever versus hypovolemia) Often the first clinical sign of hypovolemia Fluid administration as mentioned earlier
Fever	Antipyretic (acetaminophen)
Hypothermia	Passive rewarming (warm blankets, external temperature device, warm saline boluses)
Oliguria/anuria	May be marker of hypovolemia or end-organ dysfunction Target urine output is >0.5 mL/kg/h In oliguric or anuric patients, consider placement of urinary catheter for closer monitoring of urine output
Hyperglycemia	Administer regular insulin if blood sugar >200 mg/dL Goal blood sugar is 140–180 mg/dL
Anemia	Maintain hemoglobin >7 g/dL in most patients Maintain hemoglobin >8–9 g/dL if showing signs of ongoing cardiac ischemia

Managing the hospitalized patient

- The level of care will depend on the severity of sepsis, the response to antibiotics, and the initial treatment given. Patients requiring vasopressors and with hemodynamic instability should be admitted to the ICU until hemodynamically stable.
- The initial choice of antibiotics should take into consideration the risk for multidrug-resistant organisms. Risk factors for such organisms include antimicrobial therapy over the past 90 days, current hospitalization of 5 days or more, high frequency of antibiotic resistance in the community or hospital, and level of immunosuppression.
- Once cultures are resulted, antibiotics should be adjusted based on speciation and sensitivities. The length of treatment depends on the infected site/source, organism, and clinical response.

Prevention/management of complications

- Remove indwelling urinary and central venous catheters as soon as they are not needed to prevent catheter-related infections.
- De-escalate broad spectrum antibiotics as soon as possible in order to help prevent antibiotic resistance as well as *Clostridium difficile* infections secondary to antibiotic use.

Management/treatment algorithm

See Algorithm 43.1.

2018 Surviving Sepsis Campaign guidelines

These are not yet endorsed by all medical societies and are not yet incorporated into sepsis treatment protocols.

One hour bundle: to be initiated within 1 hour of sepsis recognition

- Measure lactate level*
- Obtain blood cultures before administering antibiotics
- Administer broad spectrum antibiotics (within 1 hour for severe sepsis or shock)
- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate level ≥4 mmol/L
- Apply vasopressors if hypotensive during or after fluid resuscitation to maintain MAP ≥65 mmHg

* Re-measure lactate if initial lactate is elevated (>2 mmol/L)

Six hour bundle: to be completed within 6 hours of presentation

- Re-measure lactate if initial lactate was elevated.
- Continue vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a MAP ≥65 mmHg
- If persistent hypotension despite adequate volume resuscitation or initial lactate ≥4 mmol/L, consider performing volume status reassessment via CVP and $ScvO_2$ measurement (as described by the Surviving Sepsis Campaign guidelines) or by a focused physical exam to aid in the decision to continue with fluid resuscitation or initiate vasopressors

CLINICAL PEARLS

- Key to mortality reduction is early identification and treatment.
- Initial goals of treatment include initiation of broad spectrum antibiotics, improving blood pressure with fluid resuscitation, providing respiratory support if needed, and obtaining serial lactate measurements.
- Persistent hypotension or elevated lactate despite aggressive fluid resuscitation may indicate need for vasopressors.
- Infection source control should always be addressed.

Special populations

Pregnancy/post-partum

- Maternal sepsis is the third leading cause of maternal death in the USA (13%).
- Risks include: miscarriage, abortion, Cesarean section, prolonged delivery or rupture of membranes, pre-term labor, retained products of conception.
- Pregnant patients should be hospitalized if sepsis is suspected.
- Pregnant women may already have a low blood pressure due to decreased systemic vascular resistance normally seen in the first and second trimester.
- The Sepsis in Obstetrics Score incorporates clinical criteria, modified for changes in physiology during pregnancy, to predict ICU admission for a score of 6 or higher.
- If possible, antibiotics deemed safe in pregnancy should be administered.
- Consider septic abortion as an infectious source along with other usual etiologies.
- Early consultation with an obstetrician is strongly recommended.

Elderly

- Older patients may present with more atypical or subtle features, such as weakness, lethargy, or confusion. Maintain a low threshold to rule out sepsis in these patients.
- Elderly patients with sepsis may have absence of fever or leukocytosis.
- Inquire about recent hospitalizations to determine risk for nosocomial infections.

Others

- Patients on immune-modulating agents or with immunocompromising comorbidities (e.g. HIV/AIDS, cancer, diabetes) may present with subtle signs and symptoms, if any at all. The microbial pathogen in such patients may also be more atypical or drug resistant.
- Patients on heart rate control medications (beta and calcium channel blockers) may not be tachycardic to the degree expected given the severity of infection. These patients must be treated aggressively, as their cardiac response to sepsis-induced hypotension may be limited.
- In the setting of septic shock refractory to fluids and vasopressors, consider corticosteroid administration (hydrocortisone 200 mg/day) to treat relative adrenal insufficiency.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Risk-adjusted sepsis mortality models are under development.
- Prognosis depends on severity of infection, underlying comorbidities, number of organ dysfunctions, and virulence of the pathogen.
- Serum lactate measurements are a useful prognostic tool and should be closely monitored.
- Time to antimicrobial therapy as well as control of source of infection are major determinants of risk of mortality associated with severe sepsis/septic shock.
- Recognition and understanding of the post-sepsis syndrome by providers is imperative in order to anticipate the long-term effects of sepsis and provide resources for patients.

Reading list

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Suggested websites

https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-mortality-surveillance-system.htm.
https://www.sepsis.org/sepsis-basics/post-sepsis-syndrome/.

Guidelines

National society guidelines

Title	Source	Date and weblink
2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference	SCCM/ESICM/ACCP/ATS/SIS	2003 https://doi.org/10.1007/s00134-003-1662-x
Institute for Healthcare Improvement: Severe Sepsis Bundles	Institute for Healthcare Improvement	http://www.ihi.org/resources/Pages/Tools/SevereSepsisBundles.aspx
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)	The Third International Consensus Definitions for Sepsis and Septic Shock	2016 http://jama.jamanetwork.com/article.aspx?articleid=2492881

Evidence

Type of evidence	Title and comment	Date and weblink
Prospective, randomized study	*Early Goal-Directed Therapy in the Treatment of Severe Sepsis* Introduced the concept of goal-directed therapy; proved a survival benefit when patient-centered goals were met in a timely fashion	2001 http://www.nejm.org/doi/pdf/10.1056/NEJMoa010307

(*Continued*)

Type of evidence	Title and comment	Date and weblink
RCT	*Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial* Demonstrated the non-inferiority of serial lactate measurements when compared to other, more invasive methods of monitoring response to resuscitation	2010 http://jama.jamanetwork.com/article.aspx?articleid=185405&resultClick=3
RCTs	*A Randomized Trial of Protocol-Based Care for Early Septic Shock*	2014 https://doi.org/10.1056/NEJMoa1401602
	Goal-Directed Resuscitation for Patients with Early Septic Shock	2014 https://doi.org/10.1056/NEJMoa1404380
	Trial of Early, Goal-Directed Resuscitation for Septic Shock These three trials confirmed the notion that severe sepsis can be adequately managed without the use of invasive hemodynamic monitoring or strict adherence to a management protocol. Standard therapy, however, included prompt antibiotic administration and fluid resuscitation	2015 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1500896
Retrospective study	*Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis* Found that patients can have sepsis even in the absence of two or more SIRS criteria	2015 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1415236
Retrospective study	*Duration of Hypotension Before Initiation of Effective Antimicrobial Therapy is the Critical Determinant of Survival in Human* Septic Shock Found a survival benefit when antimicrobial agents were administered within the first hour of documented hypotension	2006 https://doi.org/10.1097/01.CCM.0000217961.75225.E9

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 44

Infections Acquired in the Intensive Care Unit

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OVERALL BOTTOM LINE

- ICU-acquired infections include central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), *Clostridium difficile* infection (CDI), and pressure ulcer infection.
- Patients in ICUs have a higher risk of acquiring hospital-associated infections compared with those in non-critical care areas. ICUs are sites of significant broad spectrum antibiotic use and antibiotic-resistant pathogens are common.
- Recognition of the appropriate indications for intravascular catheter insertion, urinary catheter placement, and mechanical ventilation is paramount to prevent CLABSI, CAUTI, and VAP, respectively. Equally important is the prompt removal of these devices when no longer indicated.
- Implementation of a checklist to ensure strict adherence to evidence-based guidelines for maximum barrier precautions during catheter insertion, full compliance with bundle adherence measures, and proper hand hygiene are critical for the prevention of ICU-acquired infections.

General treatment rationale

- When an ICU-acquired infection is suspected, all devices should be removed when possible.
- Antimicrobial agents are the primary treatment. These antibiotics should be administered promptly, as a delay in treatment may lead to increased mortality.
- Choice of specific antibiotic agents should be determined by risk factors, local microbiology, and hospital-based antibiograms.
- Initial therapy should be administered intravenously with a transition to oral therapy in patients with appropriate clinical response. For *C. difficile* infection, oral treatment is preferred when possible.

General prevention

- Hand hygiene (conventional soap and water or alcohol-based hand sanitizer) and aseptic technique (maximal sterile barrier precautions with cap, mask, sterile gown, gloves, and full body drape).
- Implementation of quality improvement programs and daily assessment of bundle adherence measures for all intravascular devices, indwelling urinary catheters, and endotracheal tubes.
- All patients with suspected or laboratory confirmed *C. difficile* infections should be placed on contact precautions, utilizing barrier protection with gown, gloves, and disposable instruments (e.g. stethoscope).

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Hand hygiene with conventional soap and water is critical, as alcohol-based hand rubs do not prevent the spread of *C. difficile* spores.
- Simulation-based training can be an effective tool to instruct health care providers in the proper technique of utilizing maximal sterile barrier precautions and on the proper placement of intravascular catheters and endotracheal intubation.

Central line-associated bloodstream infections

Background

Definition of disease

- CLABSI is a laboratory confirmed bloodstream infection where a central line was in place for >2 calendar days on the date of event, with the day of device placement designated as day 1. If the central line was in place for >2 calendar days and then removed, the date of laboratory confirmed bloodstream infection must be the day of discontinuation or the following day.

Etiology

Predominant organisms are:
- Coagulase-negative staphylococci.
- *Staphylococcus aureus*.
- *Candida* species.
- Enteric Gram-negative bacilli.

Pathology/pathogenesis

- Pathogenic microbes are introduced through migration of skin organisms at the insertion site into the cutaneous catheter tract and along the surface of the catheter, with colonization of the catheter tip. This is the most common route of infection for short-term catheters.
- Direct contamination of the catheter or catheter hub, contact with hands or contaminated fluids or devices, hematogenously seeded infection from another focus of infection, and infusate contamination are less common methods of colonization and infection.

Predictive/risk factors

- Prolonged central venous or arterial catheterization.
- Skill of the operator.
- Insertion site risk factors:
  - Chlorhexidine-based solutions preferred.
  - Loss of skin integrity (e.g. burns, psoriasis).
- Submaximal barrier precautions.
- Non-tunneled greater than tunneled catheters.
- Type of catheter:
  - Number of lumens.
  - Lower risk with antibiotic impregnated catheters.
  - Greatest risk with pulmonary artery catheters.
- Repeated catheterization and use.
- Catheter site:
  - Femoral site has highest risk of infection.
  - Pre-existing infection overlying insertion site.
- Insertion circumstance:
  - Emergency greater than elective.
- Severity of illness, chronic illness, and immune deficient state:
  - Granulocytopenia.
  - Immunosuppressive chemotherapy.
- Total parenteral nutrition (TPN) administration.

Prevention

- Utilize and maintain maximal sterile barrier precautions when inserting intravascular catheters.
- Insertion site preparation:
  - 2% chlorhexidine-based solutions preferred.
  - Alternatives include iodine-based solutions.
- A subclavian or jugular site is the preferred location for central venous catheter placement. Avoid using the femoral vein for central venous access.

- The use of antiseptic/antibiotic impregnated short-term central venous catheters and chlorhexidine impregnated sponge dressings is recommended if the rate of infection is not decreasing despite adherence to other strategies.
- Catheter stabilization with a sutureless securement device is preferred to avoid disruption around the catheter entry site.
- If catheter site is bleeding or oozing, the use of sterile gauze is recommended until bleeding has resolved.
- Prompt removal of intravascular catheter when no longer indicated.

Diagnosis

Typical presentation

- Unexplained fever, leukocytosis, and decompensation in a patient with central venous or arterial access.
- Erythema, induration, and tenderness at the insertion site.

Clinical diagnosis

History

Prolonged intravascular catheterization in the presence of symptoms such as fever, chills, and rigors should increase suspicion for a catheter-associated bloodstream infection.

Physical examination

Daily examination of all catheter insertion sites for erythema, purulent discharge, and tenderness.

Laboratory diagnosis

List of diagnostic tests

- Paired aerobic and anaerobic blood cultures (at least one culture set from a peripheral vein), are collected in a sterile manner prior to the initiation of antibiotics. Skin preparation should be performed utilizing chlorhexidine.
- Quantitative catheter tip cultures have been utilized for diagnosis of CLABSI, using growth of >15 colony forming units (cfu) as positive. A positive catheter tip culture itself, however, is not sufficient for diagnosis.

List of imaging techniques

- Echocardiogram may be necessary in patients with CLABSI to evaluate for infective endocarditis.

Potential pitfalls/common errors made regarding diagnosis of disease

- Failure to implement or adhere to central line insertion checklist or full compliance with central line maintenance bundle adherence measures.
- Lack of aseptic technique in the collection of blood cultures may result in contamination and false positive cultures.

Treatment

- Duration of antibiotic therapy is dependent on pathogenic organism. Duration of antibiotics is counted from the first day of negative blood cultures.
- Vancomycin is recommended for empiric therapy due to prevalence of MRSA.
- Empiric coverage for Gram-negative organisms is recommended until cultures are available.
- Empiric coverage for multidrug-resistant (MDR) organisms is recommended for select patients:
  - Neutropenic patients.
  - Severely ill patients.
  - Known colonization with MDR pathogens.

- Empiric coverage for *Candida* species with echinocandin may be recommended for patients with certain risk factors:
  - Total parenteral nutrition.
  - Prolonged duration of broad spectrum antibiotics.
  - Hematologic malignancy.
  - Transplant recipient.
  - Colonization due to *Candida* species.
- Catheterized patients with a single positive blood culture growing coagulase-negative *Staphylococcus* species may have additional cultures collected prior to considering catheter removal.

Prognosis

Mortality from CLABSI is approximately 12–25% and is influenced by the underlying acute illness and comorbidities.

Follow-up tests and monitoring

- Patients with CLABSI require close follow-up with surveillance blood cultures to demonstrate clearance of bacteremia.
- Persistent bacteremia and/or persistent symptoms 72 hours after catheter removal with appropriate antibiotics suggest complications such as infective endocarditis and/or metastatic infections.

Catheter-associated urinary tract infections

Background

Definition of disease

- CAUTI:
  - Laboratory confirmed infection where an indwelling urinary catheter was in place for >2 calendar days on the date of event, with the day of device placement designated as day 1 and was still present on or removed the day prior to the date of event and the patient has at least one of the following signs or symptoms:
    - Fever (>38°C).
    - Urinary urgency or frequency.
    - Dysuria.
    - Suprapubic or costovertebral pain or tenderness.
    - Altered metal status.
  - Plus, positive urine culture with no more than two species of organisms with at least one species of >100 000 cfu.

Incidence/prevalence

- CAUTI is the most common healthcare-associated infection.

Etiology

- Predominant organisms are:
  - *Escherichia coli*.
  - *Enterococcus*.
  - *Candida* species.
  - *Klebsiella* species.
  - *Pseudomonas aeruginosa*.
  - *Serratia* species.
  - *Citrobacter* species.
  - *Enterobacter* species.

Long-term catheterization usually results in polymicrobial infections.

Pathology/pathogenesis

- Introduction of pathogenic microbes into the urinary system as a result of improper sterile technique with catheter placement, prolonged catheter insertion with migration of meatal, vaginal, or rectal microorganisms forming biofilms on the foreign catheter, and failure to maintain a closed drainage system are the most important mechanisms of CAUTI.
- Biofilms protect the pathogenic organism from antimicrobials and host defense mechanisms.
- Urinary stasis due to drainage failure and contamination of the urine collection bag can result in ascending infections.
- Urinary catheterization disrupts host defense mechanisms and provides access of uropathogens to the urinary system.

Predictive/risk factors for CAUTI

Duration of catheterization is one of the most significant risk factors in the development of CAUTI.

- Placement of urinary catheter for inappropriate indications.
- Repeated catheterization.
- Improper sterile technique with catheter placement.
- Failure to maintain a closed drainage system.
- Prolonged urinary catheterization.
- Advanced age.
- Female gender.
- Impaired immunity.
- Diabetes mellitus.

Prevention

- Alternative methods to internal urinary catheters such as intermittent catheterization or external catheters.
- Perform and maintain sterile technique with internal urinary catheter placement.
- Maintain a closed drainage system with unobstructed urine flow.
- The use of antiseptic impregnated urinary catheters may be considered.
- Prompt removal of internal urinary catheters when no longer indicated.

Diagnosis

Typical presentation

Unexplained fever, leukocytosis, and decompensation in a patient with indwelling urinary catheter, especially if prolonged, should trigger evaluation of a possible CAUTI.

Clinical diagnosis

History

Prolonged internal urinary catheterization in the presence of symptoms such as fever, chills, and rigors.

Physical examination

Visible erythema, tenderness, and purulent discharge from the urethral meatus, as well as purulent urine in the catheter collecting system suggest the urinary catheter as a source of infection.

Laboratory diagnosis

List of diagnostic tests

- Specimens for urine culture should only be collected when CAUTI is suspected based on abnormal urinalysis.
- Urine culture should be collected after removing the indwelling catheter and obtaining a midstream specimen.

- If the catheter cannot be removed, specimens for urine culture should be collected through a catheter port using aseptic technique.
- In patients with long-term indwelling catheters, it is recommended that a new indwelling urinary catheter be placed prior to specimen collection for urine cultures.
- Urine culture specimens should not be obtained from the urinary collecting bag.

List of imaging techniques

- Ultrasound and/or CT scan of the kidneys may be considered in patients with CAUTI who present with clinical findings of acute pyelonephritis.

Potential pitfalls/common errors made regarding diagnosis of disease

- Failure to implement or adhere to daily CAUTI prevention bundle adherence measures.
- Lack of aseptic technique in the collection of urine specimen may result in contamination and false positive cultures.

Treatment

- Prompt removal of indwelling urinary catheters.
- Empiric coverage for Gram-negative organisms is recommended until cultures are available.
- Duration of antibiotic treatment is dependent on the patient's response.

Prognosis

Mortality attributed to CAUTI is approximately 2.3% and is likely to be influenced by the underlying acute illness and comorbidities.

Follow-up tests and monitoring

All patients diagnosed with hospital-acquired infection should be closely monitored for clinical response to treatment.

Ventilator-associated event and ventilator-associated pneumonia

Background

Definition of disease

- VAE is defined as worsening oxygenation following ≥2 days of stable or decreasing FiO_2 or PEEP. There are three tiers within the VAE algorithm:
  - Ventilator-associated condition (VAC): increase in daily FiO_2 ≥20% over daily minimum FiO_2 sustained for ≥2 days or increase in PEEP of ≥3 over daily minimum PEEP for ≥2 days.
  - Infection-related ventilator-associated complication (IVAC): ≥3 days of mechanical ventilation and within 2 days of worsening oxygenation, the patient develops a temperature >38°C or <36°C, or WBC ≥12 000 or ≤4000 and a new antibiotic is started and continued for ≥4 days.
- Possible or probable ventilator-associated pneumonia (VAP): above criteria for IVAC plus positive bacterial laboratory confirmation or lung histopathology.

Etiology

Predominant organisms are:

- *P. aeruginosa*.
- *S. aureus*.
- *Klebsiella pneumoniae*.
- *Acinetobacter* species.
- *E. coli*.

Pathology/pathogenesis

- Microaspiration of oropharyngeal contents and migration of bacteria around the endotracheal tube cuff is the primary method by which bacteria invade the lower respiratory tract.
- Intubation procedure can introduce pathogenic organisms resulting in infection.
- Colonization of the endotracheal tube or the ventilator circuit by bacteria with the formation of biofilm.
- Natural host defense mechanism of secretion clearance is disrupted by the presence of an endotracheal tube and sedation.

Predictive/risk factors

- Skill of the operator performing endotracheal intubation.
- Prolonged mechanical ventilation.
- Reintubation.
- Position of endotracheal and gastric tubes. Orotracheal intubation and orogastric tubes are preferred over nasotracheal intubation and nasogastric tubes to reduce the risk of VAP.
- Risk factors for MDR organisms:
  - Antibiotic therapy in previous 90 days.
  - Current hospitalization of 2 days or more.
  - High frequency of antibiotic resistance in the community or hospital.
  - Residence in nursing home.
  - Home infusion therapy.
  - Chronic dialysis.
  - Home wound care.
  - Family member with multidrug-resistant organism.
  - Immunosuppressive disease and/or therapy.

Prevention

- Non-invasive ventilation in selected patients to prevent intubation.
- Maintain semi-recumbent position of 30–45° to prevent aspiration.
- Oral chlorhexidine to prevent oropharyngeal colonization.
- Continuous aspiration of subglottic secretions can reduce the risk of VAP.
- Endotracheal tube cuff pressure should be maintained >20 cmH_2O to prevent leakage of secretions around the cuff into the lower respiratory tract.
- Remove contaminated condensate from the ventilator circuit and prevent condensate from entering the endotracheal tube.
- Reduce the duration of mechanical ventilation and accelerate weaning through adherence to daily ventilator bundle measures.

Diagnosis

Differential diagnosis

Differential diagnosis	Features
Pulmonary embolism (PE)	Risk factors for PE No purulent secretions Negative cultures CT angiogram or V/Q scan showing PE
Congestive heart failure	Non-purulent secretions Reduced ventricular function on echocardiogram Improvement with diuretics No response to antibiotics

Differential diagnosis	Features
Pulmonary hemorrhage	Bloody secretions No response to antibiotics Bronchoscopy with hemorrhagic lavage
Atelectasis	No purulent secretions No response to antibiotics Fleeting opacities on imaging

Typical presentation

Increase in purulent secretions, fever, and worsening hypoxemia suggest VAP.

Clinical diagnosis

Physical examination

- Auscultation for the presence of crackles, wheezing, and/or egophony.
- Dullness to percussion may indicate consolidated lung or the presence of a pleural effusion.
- Daily assessment of the quality and quantity of endotracheal tube secretions

Laboratory diagnosis

List of diagnostic tests

- Lower respiratory tract secretions should be sent for culture.
  - Bronchoscopic specimen collection may be considered.
- Blood cultures should be collected prior to administration of antibiotics.
- A diagnostic thoracentesis should be performed if a patient has a moderate or large pleural effusion to rule out parapneumonic effusion or empyema.

List of imaging techniques

- Chest radiography should be performed in patients with suspected VAP to:
  - Define severity of pneumonia.
  - Identify presence of complications such as effusion or cavitation.
- Chest ultrasonography may be obtained in institutions with appropriate ultrasound expertise.

Potential pitfalls/common errors made regarding diagnosis of disease

- Failure to maintain accurate duration dates for mechanical ventilation.
- Failure to implement or fully adhere to daily ventilator bundle measures.
- Lack of proper technique in the collection of tracheal aspirate or bronchoscopic specimen may result in contamination and/or inadequate specimen.

Treatment

- Antibiotic therapy is recommended in patients with no known risk factors for MDR pathogens (Table 44.1).
- Combination antibiotic therapy is recommended in patients with suspected MDR pathogens (Table 44.2).
- Duration of appropriate antibiotic treatment for VAP in a patient with appropriate clinical response is 7 days.
- *P. aeruginosa* should be treated for at least 14 days.
- Aerosolized antibiotics may be considered as adjunctive therapy in patients with VAP due to MDR Gram-negative pathogens not responding to intravenous therapy.

Prognosis

Mortality attributed to VAP has been reported prior to the new VAE definition to be approximately 13% and is likely to be influenced by the underlying acute illness and comorbidities.

Table 44.1 Initial empiric antibiotic therapy for suspected VAP in patients with no known risk factors for MDR pathogens.

Suspected pathogen	Recommended empiric antibiotic
Streptococcus pneumoniae *Haemophilus influenzae* MRSA	Ceftriaxone *Or* Levofloxacin/moxifloxacin
Sensitive enteric Gram-negative bacilli: • *E. coli* • *K. pneumoniae* • *Enterobacter* • *Proteus* • *Serratia*	Ampicillin/sulbactam

Table 44.2 Initial empiric antibiotic therapy for suspected VAP in patients *with* risk factors for MDR pathogens.

Suspected MDR pathogen	Recommended combination antibiotic therapy
Pseudomonas aeruginosa *Klebsiella pneumoniae* *Acinetobacter* species Methicillin-resistant *Staphylococcus aureus* (MRSA)	Antipseudomonal cephalosporin *Or* Antipseudomonal carbapenem *Or* Antipseudomonal β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) *Plus* Vancomycin or linezolid

Clostridium difficile infection

Background

Definition of disease

- CDI is one of the main causes of antibiotic-associated diarrhea in hospitalized patients. Diagnosis is based on a combination of clinical and laboratory findings in patients with current or recent health care exposure.
- The most common clinical finding is diarrhea:
  - ≥3 unformed stools within a 24 hour period.
  - The Bristol stool scale can be used in the initial assessment: ≥3 stools is categorized as type 5 or greater within 48 hours or 1 stool is categorized as type 7 (watery) within the past 24 hours.
- Laboratory confirmation with either a positive test on an unformed stool specimen for toxin-producing *C. difficile* or direct colonoscopic visualization with findings revealing pseudomembranous colitis.

Etiology

Clostridium difficile is an anaerobic organism responsible for the majority of cases of antibiotic-associated colitis.

Pathology/pathogenesis

- CDI is the result of person-to-person spread through the fecal–oral route. The most important mechanism by which *C. difficile* is spread is through the hands of health care workers contaminated with *C. difficile* spores.

- Antimicrobial therapy results in alteration of the normal intestinal flora, predisposing patients to the development of *C. difficile* colitis.
- Pathogenic *C. difficile* produces two distinct toxins. Toxin A is an enterotoxin and toxin B is a cytotoxin. Both toxins bind to the intestinal mucosal cells resulting in mucosal inflammation and the development of pseudomembranous colitis. This mucosal inflammation leads to diarrhea (bloody or non-bloody), and in severe cases, ileus with toxic megacolon.
- NAP1 is a hypervirulent strain of *C. difficile* most commonly associated with severe and fulminant colitis.
- Asymptomatic *C. difficile* colonization is common, with an estimated prevalence of 7–26% in acute care facilities.

Predictive/risk factors

- Inappropriate use of antibiotics. Any antibiotic can predispose to CDI. The most frequently implicated antibiotics include clindamycin, fluoroquinolones, and cephalosporins.
- Hospitalization.
- Advanced age >70 years.
- Severe illness and impaired immunity:
  - Chemotherapy.
  - Hematopoietic stem cell transplant.
  - Gastrointestinal surgery.
- Use of proton pump inhibitors.
- Failure to utilize appropriate contact precautions and disposable medical devices, as well as improper hand hygiene.
- Improper sterilization of rooms and equipment after exposure.

Prevention

Screening

- Stool culture, enzyme immunoassay (EIA) for *C. difficile* toxin, or PCR of liquid stool sample in patients with risk factors and new onset diarrhea.

Primary prevention

- Antibiotic stewardship. Optimize the use and duration of antibiotic therapy to minimize unnecessary antibiotic exposure.
- Early detection and contact isolation precautions:
  - Use of private rooms is recommended.
  - Gloves and gowns should be worn upon room entry and removed prior to exiting the room.
  - Strict adherence to hand hygiene with conventional soap and water. Instruct visitors on the necessity of hand hygiene.
  - Dedicated disposable medical equipment should be utilized.
  - Contact precautions should be maintained for the duration of diarrhea.
- Environmental cleansing with chlorine-based agents is recommended.

Secondary prevention

- Antimicrobial therapy:
  - Prolonged course of oral vancomycin with a gradual taper in recurrent disease.
- Fidaxomicin may be considered for recurrent disease.
- Fecal microbiota therapy (FMT):

- Indications:
  - Recurrent or relapsing infection:
    - ≥3 episodes of mild–moderate CDI and failure of 6–8 week vancomycin taper.
    - ≥2 episodes of severe CDI.
  - Persistent moderate (>1 week) or severe (>48 hours) CDI not responding to appropriate therapy.
  - Protracted CDI:
    - ≥3 weeks of ongoing symptoms on appropriate antimicrobial therapy.
- Absolute contraindications to FMT:
  - Decompensated liver cirrhosis.
  - HIV/AIDS.
  - Bone marrow transplant recipients.
  - Severe immunodeficiency.
  - Anaphylactic food allergy which was not excluded from donor diet.
- FMT may be delivered by colonoscopy or flexible sigmoidoscopy.
- Repeat FMT may be considered if inadequate response to initial FMT therapy.

Diagnosis

Differential diagnosis

Differential diagnosis	Features
Acalculous cholecystitis	Right upper quadrant (RUQ) tenderness Hepatic function panel with cholestatic profile RUQ ultrasound or HIDA scan showing cholecystitis
Infectious diarrhea (not due to *C. difficile*)	Negative *C. difficile* testing Stool culture positive for other organism May have bloody or non-bloody diarrhea No significant antibiotic exposure or recent hospitalization
Ischemic colitis	Patient risk factors for ischemia Acute onset No significant antibiotic exposure or recent hospitalization May have bloody or non-bloody diarrhea Elevated lactate Negative *C. difficile* testing

In CDI, diarrhea (mucus, bloody, or non-bloody) remains the most common clinical presentation, especially in the setting of antibiotic use or recurrent hospitalization. Ileus due to CDI may present as abdominal pain and distension without associated diarrhea.

Clinical diagnosis

History

- Patient reports of bloody or non-bloody diarrhea with recent hospitalization, antibiotic exposure, or contact with an individual known to have *C. difficile* should raise awareness regarding possible CDI.

Physical examination

- Observation for bloody or mucus/non-bloody diarrhea. Auscultation for bowel sounds should be performed to assess for ileus. Examination and palpation of the abdomen for distension and tenderness to evaluate for progression to ileus and megacolon.

Disease severity classification

- Mild to moderate:
  - White blood cell count <15 000/mm^3.
  - Serum creatinine <1.5 times baseline.
- Severe:
  - White blood cell count ≥15 000/mm^3.
  - Serum creatinine ≥1.5 times baseline.
- Severe and complicated:
  - White blood cell count ≥15 000/mm^3.
  - Serum creatinine ≥1.5 times baseline.
  - Hypotension or shock.
  - Ileus or megacolon.

Laboratory diagnosis

List of diagnostic tests

- Testing for *C. difficile* should be performed only on unformed stool, unless ileus from *C. difficile* is suspected.
- Stool culture is the most sensitive test to detect CDI. It is limited by a slow turnaround time.
- EIA testing for *C. difficile* toxins A and B is rapid, but is less sensitive than stool culture.
- PCR testing is rapid, sensitive, and specific.
- Two-step testing may be considered to increase diagnostic accuracy.
- Colonoscopy with biopsy may be performed to identify pseudomembranous colitis.

List of imaging techniques

- Abdominal radiography (X-ray or CT scan) should be obtained if complications of CDI such as ileus, megacolon, or perforation are suspected.

Potential pitfalls/common errors made regarding diagnosis of disease

- Lack of consideration for CDI. Delay in testing and diagnosis can result in significant delay in treatment and spread of infection.
- CDI is a clinical diagnosis with confirmatory laboratory findings. Sending *C. difficile* stool specimens without appropriate clinical symptoms may result in identification of *C. difficile* carrier state, which does not require treatment.

Treatment

- CDI is characterized as non-severe, severe, fulminant or recurrent.
- A surgical consultation should be obtained in patients with severe CDI.

Clinical definition	Clinical data	Treatment
Initial episode, non-severe disease	WBC < 15 000/mm^3 and serum creatinine level < 1.5 times baseline	Oral vancomycin 125 mg four times per day or oral fidaxomicin 200 mg twice daily, 10 days
Inital episode, severe	WBC ≥ 15 000/mm^3 or serum creatinine level ≥ 1.5 times baseline	Oral vancomycin 125 mg four times per day or oral fidaxomicin 200 mg twice daily, 10 days
Inital episode, fulminant	Hypotension or shock, ileus, megacolon	Oral vancomycin 500 mg four times per day, plus intravenous metronidazole 500 mg every 8 hours. If ileus, consider adding rectal vancomycin
First recurrence		Same as initial treatment
Second recurrence		Vancomycin in tapered or pulsed regimen

Prognosis

- Mortality attributed to health care-associated CDI ranges from 6% to 30%.
- Infection with hypervirulent strain NAP1/BI/027 may result in more severe disease and higher mortality.

Natural history of untreated disease

- The course of untreated CDI is dependent on the severity of disease, strain of *C. difficile*, and the underlying immune function of the patient.
- Untreated patients may have increasingly voluminous diarrhea, develop ileus, and progress to toxic megacolon with potential perforation and development of an overwhelming septic state.

Follow-up tests and monitoring

- Repeat testing during the same episodes of diarrhea is not recommended.
- Test of cure following treatment of *C. difficile* is not recommended.

Pressure ulcer infection

Background

Definition of disease

- A laboratory confirmed superficial or deep skin or soft tissue infection with at least two of the following signs or symptoms with identifiable risk factor(s): erythema, edema, or tenderness of the wound edges.
  - Plus, organisms identified from tissue biopsy or aspiration of fluid from the ulcer margin.

Etiology

Predominant organisms are:

- *Enterobacter* species.
- Staphylococci.
- *Enterococcus faecalis*.

Pathology/pathogenesis

- Pressure ulcers develop due to localized injury to the skin and/or soft tissue. These injuries typically occur over bony prominences as a result of sustained pressure and/or friction.
- Breakdown of the skin barrier from a combination of pressure, friction, shearing forces, and moisture predisposes to bacterial colonization and the development of skin and soft tissue infections.
- Externally applied pressure on body surfaces exceeds the capillary perfusion pressure within the tissue. This disrupts the microcirculation resulting in inflammation, free radical generation, and hypoxic tissue necrosis.

Predictive/risk factors

- Immobility.
- Malnutrition.
- Reduced perfusion:
  - Peripheral arterial disease.
  - Congestive heart failure.
- Sensory loss:
  - Spinal cord injury.
  - Neuropathy.
- Moisture.

Prevention

Screening

Risk assessment and a complete skin assessment should be conducted on all patients admitted to the ICU and repeated as required based on risk factors and patient acuity.

Primary prevention

- Cushion dressings should be applied to areas of high risk to protect the skin.
- Daily skin inspection.
- Frequent repositioning of immobile, bedbound patients with maintenance of dry skin environment.

Diagnosis

Typical presentation

Pressure ulcer infections typically present with erythema, edema, and tenderness with or without purulent discharge, on an area of the body vulnerable to pressure ulcers.

Clinical diagnosis

History

Prolonged immobility and infectious symptoms should raise concern for pressure ulcer infection.

Physical examination

Daily assessment of pressure ulcers for depth, visible erythema, edema, purulent discharge, or visible bone.

Disease severity classification

Pressure ulcers are categorized into stages:
- Stage I: non-blanchable erythema with intact skin.
- Stage II: partial thickness loss of dermis with red-pink wound bed.
- Stage III: full thickness skin loss. Subcutaneous fat may be visible in areas of adipose tissue.
- Stage IV: full thickness tissue loss with exposed tendon, muscle, and/or bone.
- Unstageable: full thickness skin or tissue loss with depth unknown.

Laboratory diagnosis

- Cultures should be collected either by tissue biopsy or aspirate of fluid at the ulcer margin.
- MRI, CT scan, and/or bone scans are recommended in patients with infected pressure ulcers with high clinical suspicion for osteomyelitis.

Potential pitfalls/common errors made regarding diagnosis of disease

- Failure to perform a thorough daily skin assessment in patients at high risk for pressure ulcers or with existing pressure ulcers

Treatment

- Pain control.
- Local wound care.
- Consultation of wound care professional.
- Intravenous antibiotics.
- Patients with pressure ulcer infections and evidence of tissue necrosis should have surgical consultation and debridement.

Prognosis

Natural history of untreated disease

- Neglected pressure ulcers will progress in severity.
- Bone involvement may result in osteomyelitis. Secondary bacteremia may develop and can progress to a potentially lethal septic state.

Follow-up tests and monitoring

- Patients treated for pressure ulcer infections should have frequent skin examinations to ensure appropriate healing.

Reading list

Dudeck MA, et al. National Healthcare Safety Network report, data summary for 2013, device-associated module. Am J Infect Control 2015;43(3):206–21.

Yokoe DS, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. Infect Control Hosp Epidemiol 2014;35(8):967–77.

Zimlichman E, et al. Health care-associated infections. A meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013;173(22):2039–46.

Suggested websites

http://www.cdc.gov/drugresistance/
http://www.cdc.gov/hai/
http://www.cdc.gov/nhsn/
http://www.idsociety.org/IDSA_Practice_Guidelines/
http://www.npuap.org/

Guidelines

National society guidelines

Title	Source	Date and reference/weblink
Guidelines for the Prevention of Intravascular Catheter-Related Infections	Centers for Disease Control and Prevention (CDC)	2011 https://www.cdc.gov/infectioncontrol/guidelines/BSI/index.html
Strategies to Prevent Catheter-Associated Urinary Tract Infections in Acute Care Hospitals: 2014 Update	IDSA	2014 Lo E, et al. Infect Control Hosp Epidemiol 2014;35(5):464–79
Guidelines for the Management of Adults with Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia	American Thoracic Society (ATS) and IDSA	2005 ATS; IDSA. Am J Respir Crit Care Med 2005;171:388–416
Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals	Society for Healthcare Epidemiology of America (SHEA) and IDSA	2008 Coffin SE, et al. Infect Control Hosp Epidemiol 2008;29: S31–40
Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update	SHEA and IDSA	2018 McDonald LC, et al. Clin Infect Dis 2018;66(7):e1–48
Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline	National Pressure Injury Advisory Panel (NPUAP), EPUAP, and PPPIA	2014 http://www.npuap.org/

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

with website

CHAPTER 45

Antimicrobial Therapy

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OVERALL BOTTOM LINE

- Due to the high number of complicated and difficult to treat infections in critical care units, in-depth knowledge of antimicrobial agents is required.
- Critically ill patients require individualized dosing and therapeutic drug monitoring because of their altered ability to absorb, distribute, metabolize, and eliminate antimicrobials.
- In choosing empiric antimicrobial therapy, the clinician must consider the most likely site and organism responsible for the infection, in addition to hospital susceptibility data, potential adverse effects, cost effectiveness, and recent antibiotic exposure.
- The incidence of multidrug-resistant bacterial pathogens isolated in ICUs is increasing and is associated with increased ICU morbidity, mortality, and cost.
- Antimicrobial stewardship programs (ASPs) have become the modern approach to optimizing the administration of antimicrobials through appropriate selection, dosing, monitoring, reassessment, and de-escalation.

Background

- Infection in ICUs is associated with considerable morbidity, mortality, and expense.
- About 50% of patients in ICUs are infected and about 70% receive antibiotics.
- The costs associated with infection may account for as much as 40% of total ICU expenditures.
- When designing an antimicrobial regimen, the pharmacology of anti-infectives involves many factors.
  - Organism: local susceptibility patterns, minimum inhibitory concentration (MIC), resistance mechanisms.
  - Drug: pharmacokinetics, pharmacodynamics (PD), tissue penetration, potential adverse effects, interactions, resistance, cost.
  - Host: source and site of infection, recent antimicrobial therapy, allergies, age, weight, organ function, comorbidities, immunocompromised state, concomitant therapy, pregnancy.
- See Table 45.1 for guidelines regarding the empiric selection of antimicrobials for the most common infections based on the most likely organism responsible for the infection.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Table 45.1 Guide to empiric antimicrobial therapy in the critical care unit.

Type of infection	Common pathogens	Empiric selection	Clinical pearls
Bacterial meningitis			
2–50 years old	*Neisseria meningitidis*, *Streptococcus pneumoniae*	Vancomycin plus ceftriaxone or cefotaxime ± rifampin (with steroids only)	Duration of treatment: Pneumococcus: 10–14 days Listeria: ≥21 days
>50 years old	*S. pneumoniae*, *N. meningitidis, Listeria monocytogenes*, aerobic Gram-negative bacilli	Ampicillin plus vancomycin plus ceftriaxone or cefotaxime ± rifampin (with steroids only)	
Post-neurosurgery or penetrating trauma	Aerobic Gram-negative bacilli (including *Pseudomonas aeruginosa), Staphylococcus aureus,* coagulase-negative staphylococci	Vancomycin plus cefepime or ceftazidime or meropenem	
Intravascular catheter-related blood stream infection			
Not neutropenic or septic	Coagulase-negative staphylococci, *S. aureus*	Vancomycin or daptomycin (if high rates of MRSA with vancomycin MIC >2 mg/L)	Catheter should be removed in sepsis and/or presence of a virulent pathogen
Neutropenia or sepsis	Above plus Gram-negative bacilli (GNB) including *P. aeruginosa*	Vancomycin plus cefepime or piperacillin-tazobactam	
	Consider empiric treatment of candidemia for patients with: total parenteral nutrition, prolonged exposure to antibiotics, hematologic malignancy, organ transplantation, femoral catheterization, or colonization due to *Candida* species	Echinocandin (or fluconazole in selected patients)	

***Clostridium difficile* infection (CDI) – initial episode**			
Asymptomatic colonization (positive *C. difficile* test without diarrhea, ileus, or colitis)	*Clostridium difficile*	No treatment	
Non-severe disease (positive *C. difficile* test with diarrhea, WBCs ≤15 000/mm3 and serum creatinine <1.5 mg/dL)		PO vancomycin or fidaxomicin	Duration of treatment: 10 days
Severe (e.g. WBCs > 15 000/mm3 or serum creatinine ≥ 1.5 mg/dL)		PO vancomycin or fidaxomicin	Early surgical consultation
Fulminant (hypotension or shock, ileus, megacolon)		PO vancomycin plus IV metronidazole ± vancomycin retention enema (500 mg/100 mL normal saline every 6 hours)	Surgical consultation
Febrile neutropenia			
Inpatient IV antibiotics (high risk – anticipated neutropenia >7days, clinically unstable or medical comorbidities)	Gram-positive cocci (GPC) (staphylococci, streptococci) GNB (including *P. aeruginosa*), rarely anaerobes	Piperacillin/tazobactam or imipenem or meropenem or cefepime or ceftazidime	
Catheter-related, skin and soft tissue infections, pneumonia or hemodynamic instability	GPC, GNB, MRSA	Beta-lactam as above plus vancomycin	
Abdominal symptoms	GPC, GNB, anaerobes	Beta-lactam as above plus metronidazole for additional anaerobic coverage	
Febrile after 4–7 days on broad spectrum antibiotics	GPC, GNB, fungus (*Candida* sp, *Aspergillus* sp.)	Consider empiric antifungal coverage: echinocandin or voriconazole or amphotericin B preparation	
Febrile >4 days and hemodynamically unstable	Resistant GPC, GNB, anaerobes, fungus	Antifungal coverage as above Coverage for resistant bacteria	
Spontaneous bacterial peritonitis	Enterobacteriaceae, *S. pneumoniae,* enterococci	Cefotaxime or ceftriaxone or piperacillin-tazobactam	Can use other regimens which cover Gram-negative aerobic and anaerobic organisms
Secondary peritonitis (e.g. bowel perforation, ruptured appendix)	Enterobacteriaceae, *Bacteroides* sp., enterococci, *P. aeruginosa*	Piperacillin-tazobactam or cefepime plus metronidazole or ciprofloxacin plus metronidazole	

(*Continued*)

Table 45.1 (*Continued*)

Type of infection	Common pathogens	Empiric selection	Clinical pearls
Pneumonia			
Community-acquired pneumonia admitted to ICU	*S. pneumoniae*, *Legionella* sp., *Haemophilus influenzae*, Enterobacteriaceae, *S. aureus*, atypical respiratory pathogens	A beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone	
	Above plus risk for *P. aeruginosa*	Piperacillin-tazobactam or cefepime or imipenem or meropenem plus ciprofloxacin or levofloxacin or Above beta-lactam plus an aminoglycoside plus either azithromycin or a fluoroquinolone	
Hospital-acquired pneumonia	Average risk of *P. aeruginosa* or other GNB	Cefepime or piperacillin-tazobactam or levofloxacin or imipenem or meropenem	Initial therapy should be based on knowledge of local pathogens and susceptibility patterns
	Risk factors increasing likelihood of *P. aeruginosa* or other GNB or high risk of mortality	Prescribe antibiotics from two different classes with antipseudomonal activity as above. May include an aminoglycoside or aztreonam in regimen	
	Risk factors for MRSA or high mortality risk	Above regimen plus vancomycin or linezolid	Duration of treatment: 7 days
Ventilator-associated pneumonia	*S. aureus, P. aeruginosa, Klebsiella pneumoniae*, *Acinetobacter* sp., other Gram-negative bacilli	Cefepime or ceftazidime or imipenem or meropenem or piperacillin-tazobactam	Duration of treatment: 7 days
	Risk factors for antimicrobial resistance	Consider adding ciprofloxacin or levofloxacin an aminoglycoside or polymyxin or colistin	
	Risk factors for MRSA	Above plus vancomycin or linezolid	
Complicated pyelonephritis			
Complicated pyelonephritis (e.g. patients with diabetes mellitus, renal failure, urinary tract obstruction, indwelling urethral catheter, stent, nephrostomy tube, urinary diversion, immunosuppression, or transplantation)	*Escherichia coli*, other *Enterobacteriaceae*, *P. aeruginosa*, enterococci, *S. aureus*	Mild or moderate disease: ceftriaxone or ciprofloxacin or levofloxacin Severe disease: cefepime or piperacillin-tazobactam or meropenem or imipenem	If resistance on prior urinary cultures, use broader or more appropriate agent Ceftriaxone and cefepime do not cover enterococci
Skin and soft tissue			
Necrotizing fasciitis	Streptococci sp. (group A, C, G), *Clostridia* sp., polymicrobial (aerobic + anaerobic), *S. aureus, K. pneumoniae*	Vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem plus clindamycin	Clindamycin is added for antitoxin effects

Clinical pharmacology principles

Understanding the basic clinical pharmacology of antimicrobials will help guide therapy.

Bactericidal versus bacteriostatic pharmacodynamics

- The relationship between antibiotic activity and various bacterial species may be characterized as bactericidal or bacteriostatic. This applies to in vitro testing for a particular microbial strain.
- Using in vitro microbiologic techniques:
  - Bactericidal activity is defined as a $\geq$3-$\log_{10}$ cfu/mL reduction in 24 hours or by the ratio of minimum bactericidal concentration (MBC)/MIC $\leq$4.
  - Bacteriostatic activity is <3-$\log_{10}$ cfu/mL reduction in 24 hours or the MBC/MIC >4.
- In general, concentrations that reach bactericidal activity are preferred for severe infections that may progress rapidly with potential lethal consequences. A disadvantage of rapid bacterial killing may be the release of cell wall components, endotoxins, and cytokines.

Key pharmacodynamic predictors of antibiotic effectiveness

- Concentration (peak) dependent activity:
  - Serum concentration reaches an adequate peak regardless of the concentration at the end of the dosing interval (e.g. gentamicin peak concentration $\geq$10 times MIC).
  - Goal is to maximize peak concentration yet limit the time of exposure.
  - Common antibiotics include aminoglycosides and polymyxins.
- Time-dependent activity:
  - Serum concentration adequately maintained above the MIC for the entirety of the dosing interval.
  - Goal is to maximize duration of exposure.
  - Common antibiotics include penicillins, cephalosporins, and carbapenems.
- Concentration/time-dependent activity:
  - Another measure of exposure to an antibiotic is the area under the curve (AUC) : MIC, which is becoming more widely used as a predictor of drug effectiveness.
  - Goal is to maximize total amount of exposure.
  - Common antibiotics include fluoroquinolones, linezolid, macrolides, clindamycin, tetracyclines, and vancomycin.

Dosing principles using pharmacokinetics

- The loading (first) dose (LD) is designed to achieve an initial serum concentration that mimics an effective steady state concentration.
- The LD is usually a relatively higher dose than that of the maintenance dose (MD).
- The MD regimen takes into account patient physiologic factors and microbial factors that account for the rate and extent of elimination.
  - Patient factors in the critically ill include weight, fluid shifts, renal function, liver function, extracorporeal membrane oxygenation (ECMO), and sepsis.
  - Microbial factors include susceptibility to the agent and site of infection (e.g. lung, brain, heart, urinary tract) such that different doses and serum concentrations may be needed for different sites of infection.
  - Higher MD therapy may be more appropriate in morbidly obese or neutropenic patients, in those with infection involving sites in which drug penetration is poor (e.g. meninges, heart), or in those with infection involving organisms with increased MIC susceptibility.
  - Extended infusions with shorter dosing intervals of time-dependent killing antimicrobials (e.g. cefepime, piperacillin/tazobactam, meropenem) are being used more often because they potentially optimize attainment of target concentrations.

- The MD regimen for concentration-dependent agents differs from time-dependent regimens.
  - Each dose is intended to achieve a high peak concentration relative to the MIC, with very low trough concentrations that are sometimes intended to be undetectable.
  - Higher initial doses may be needed when extracellular water is increased, such as with edema, septic shock, post-surgery, or trauma.
  - High concentration extended-interval aminoglycoside dosing as opposed to traditional dosing is an example of this dosing technique.

Pathophysiologic and pharmacokinetic changes in the critically ill

The primarily affected pharmacokinetic parameters are distribution and elimination.

- Changes in serum proteins affect distribution of protein-bound agents (e.g. ceftriaxone, clindamycin, doxycycline, nafcillin, tigecycline, vancomycin).
- Hydrophilic agents tend to have low volumes of distribution, are primarily renally eliminated, and have relatively low intracellular tissue penetration (e.g. aminoglycosides, beta-lactams, polymyxins, vancomycin).
- Lipophilic agents tend to have wider volumes of distribution, are primarily hepatically eliminated, and have relatively higher intracellular tissue penetration (e.g. macrolides, lincosamides, tetracyclines, tigecycline).

Specific treatments

Acute renal failure requiring IHD, CRRT, and PD

- Factors affecting antimicrobial use include the degree and rapidity of renal impairment, type and duration of dialysis, intrinsic residual function, and drug pharmacology and interactions.
- Common methods of continuous renal replacement therapy (CRRT) in the critically ill are continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF), and peritoneal dialysis (PD).
- Specific factors that may influence dosing with intermittent hemodialysis (IHD)/CRRT/PD include:
  - Flow rate: increasing the blood or dialysate flow rate will increase drug clearance.
  - Membrane pore size (sieving coefficient): larger pores allow removal of drugs with larger molecular weight.
  - Protein binding: antimicrobials with low protein binding capacity in serum may be removed.
  - Distribution: reduced drug removal by IHD/CRRT occurs with agents that have larger volumes of distribution.
  - Sepsis: dosing is further affected by changes in cardiac output, fluid shifts, capillary permeability, and end-organ dysfunction.
- Table 45.2 includes dosing considerations for IHD/CRRT/PD:
  - For CRRT dosing ranges, higher daily doses may be needed for CVVHDF, moderate doses for CVVHD, and lower doses for CVVH.
  - Dosing regimens used with IHD cannot be consistently employed with CRRT.
- Obtaining therapeutic drug monitoring concentrations:
  - IHD: trough preferably prior to IHD; or following a session, ≥2 hours for aminoglycosides and ≥4–6 hours for vancomycin to allow for drug redistribution.
  - CRRT: aminoglycoside peak concentration should be 2 hours after the dose and random concentrations at steady state after the third dose.
  - Monitor a 24 hour random concentration and every 3–5 days once an acceptable dosing regimen is established.

Table 45.2 Pharmacotherapy for common antibiotics in critical care.

Generic name	General spectrum of activity	Usual initial dosing for critically ill	Route of administration	Renal dose adjustments	Clinical pearls
Penicillins (w/ & w/o beta-lactamase inhibitors) MOA: binds to penicillin-binding proteins inhibiting peptidoglycan cell wall synthesis resulting in cellular lysis Net effect: bactericidal activity					
Ampicillin	GPC GNB	1–2 g q4–6 h IHD: 1–2 g q12–24 h CRRT: load 2 g MD 1–2 g q6–12 h	IV	Yes	Higher dose for *Listeria* meningitis recommended Limited Gram-negative organism coverage
Ampicillin/ sulbactam	GPC GNB (no PA) Anaerobes	1.5–3 g q6 h IHD: 1.5–3 g q8–12 h CRRT: load 3 g MD 1.5–3 g q6–12 h	IV	Yes	Sulbactam is a sulfonamide molecule that may cause allergenic cross-reactivity with other sulfonamides Sulbactam often maintains susceptibility to *Actinetobacter baumannii*
Amoxicillin/ clavulanate	GPC GNB (no PA) Anaerobes	875 mg/125 mg q12 h	PO	Yes	
Nafcillin	GPC (MSSA)	1–2 g q4 h IHD/CRRT: same	IV	No	Recommended 12 g/day for bacteremia Extravasation can result in tissue necrosis; may cause neutropenia
Oxacillin	GPC (MSSA)	1–2 g q4 h IHD/CRRT: same	IV	No	Recommended 12 g/day for bacteremia Reversible increase of transaminases
Piperacillin/ tazobactam	GPC GNB (PA) Anaerobes	3.375–4.5 g q6 h IHD: 2.25 g q8–12 h CRRT: 2.25–3.375 g q6–8 h	IV	Yes	Tazobactam is a sulfonamide molecule that may cause allergenic cross-reactivity with other sulfonamides Extended infusion of 4 hours q8 h may be more effective than 30 minute infusions q6 h If MIC to *Pseudonomas aeruginosa* is 32–64 mg/L, consider switch to cefepime or meropenem
Cephalosporins (w/ & w/o beta-lactamase inhibitors) MOA: binds to penicillin-binding proteins inhibiting peptidoglycan cell wall synthesis resulting in cellular lysis Net effect: bactericidal activity					
Cefazolin (first generation)	GPC GNB	1–2 g q8 h IDH: 500 mg to 1 g q24 h CRRT: load 2 g MD 1 g q8 h or 1–2 g q12 h	IV	Yes	Limited Gram-negative organism coverage

(*Continued*)

Table 45.2 (*Continued*)

Generic name	General spectrum of activity	Usual initial dosing for critically ill	Route of administra-tion	Renal dose adjustments	Clinical pearls
Cefoxitin (second generation)	GPC GNB (no PA) Anaerobes	1–2 g q6–8 h	IV	Yes	Increasing resistance to *Bacteroides fragilis*
Ceftriaxone (third generation)	GPC GNB (no PA) Oral anaerobes	1–2 g q12–24 h IHD: 1–2 g q24 h CRRT: load 2 g MD same	IV/IM	No	May cause biliary sludge in gallbladder
Cefpodoxime (third generation)	GPC GNB (no PA)	200–400 mg q12 h	PO	Yes	Possible agent to convert ceftriaxone from IV to PO
Ceftazidime (third generation)	GPC GNB (PA)	1–2 g q8–12 h IHD: 500 mg to 1 g q24 h CRRT: load 2 g MD 1 g q8 h or 1–2 g q12 h	IV	Yes	
Cefepime (fourth generation)	GPC GNB (PA)	1–2 g q12 h IHD: 500 mg to 1 g q24 h CRRT: load 2 g MD 1 g q8 h or 1–2 g q12 h	IV	Yes	Seizure risk with ESRD *P. aeruginosa* dose 1–2 g q8 h
Ceftaroline (fifth generation)	GPC (MRSA, DRSP)	600 mg q12 h IHD: 200 mg q12 h	IV	Yes	
Ceftazidime/avibactam (third generation/BLI)	GPC GNB (PA)	2.5 g q8 h	IV	Yes	Avibactam is a non-beta-lactam beta-lactamase inhibitor that reconfers susceptibility to ceftazidime Used for some multidrug-resistant organisms, possibly in a multidrug regimen
Ceftolozane/tazobactam	GPC GNB	1.5 g q8 h IHD: 750 mg once, then 150 mg q8 h	IV	Yes	Not active against KPC-producing bacteria; active against some Enterobacteriaceae and *P. aeruginosa* isolates with certain mechanisms of resistance
Carbapenems MOA: binds to penicillin-binding proteins inhibiting peptidoglycan cell wall synthesis resulting in cellular lysis Net effect: bactericidal activity					

Ertapenem	GPC GNB (no PA) Anaerobes	1 g q24 h	IV	Yes	Seizure risk Induces valproic acid metabolism – avoid concomitant use
Imipenem/cilistatin	GPC GNB (PA) Anaerobes	500 mg q6 h IHD: 250–500 mg q12 h CRRT: load 1 g MD 500 mg 6–8 h	IV/IM	Yes	Seizure risk Induces valproic acid metabolism – avoid concomitant use
Meropenem	GPC GNB (PA) Anaerobes	1 g q8 h or 500 mg q6 h IHD: 500 mg q24 h CRRT: load 1 g MD 500 mg to 1 g q8–12 h PD: recommended dose q24 h	IV	Yes	Seizure risk Induces valproic acid metabolism – avoid concomitant use Extended infusion of 1 g over 3 hours q8 h may be more effective than 500 mg over 30 minutes q6 h or 1 g over 30 minutes q8 h
Monobactam MOA: binds to penicillin-binding proteins inhibiting peptidoglycan cell wall synthesis resulting in cellular lysis Net effect: bactericidal activity					
Aztreonam	GNB (PA)	1–2 g q8 h IHD: 500 mg q12 h CRRT: load 2 g MD 1 g q8 h or 1–2 g q12 h	IV	Yes	Alternative for beta-lactam allergy; confers no activity against Gram-positive organisms or anaerobes
Fluoroquinolones MOA: inhibits DNA-gyrase thus not allowing supercoiled DNA uncoiling and promotes double-strand DNA breakdown Net effect: bactericidal activity					
Ciprofloxacin	MSSA GNB (PA) Atypical lung pathogens	400 mg q8–12 h IHD: 200–400 mg q24 h CRRT: 200–400 mg q12–24 h PD: 500 mg q24 h	IV PO	Yes	Prolongs QTc interval Excellent tissue penetration Enteral absorption interactions with di- or trivalent cations, multivitamins, antacids, tube feeds
Levofloxacin	GPC GNB (PA) Atypical lung pathogens	750 mg q24 h IHD: 250–500 mg q48 h CRRT: load 500–750 mg MD 250–750 mg q24 h	IV PO	Yes	Ciprofloxacin is the most reliable for empiric *P. aeruginosa* coverage
Moxifloxacin	GPC GNB Anaerobes Atypical lung pathogens	400 mg q24 h IHD/CRRT: same	IV PO	No	

(*Continued*)

Table 45.2 (*Continued*)

Generic name	General spectrum of activity	Usual initial dosing for critically ill	Route of administration	Renal dose adjustments	Clinical pearls
Lincosamide MOA: binds to the 50S ribosomal subunit (reversibly), preventing peptid–bond formation and inhibiting protein synthesis Net effect: bacteriostatic activity					
Clindamycin	GPC Anaerobes	600–900 mg q8 h IHD/CRRT: same	IV PO	No	Good tissue penetration including bone, minimal CSF penetration; among the most common offenders of *C. difficile* infections
Macrolides MOA: inhibits protein synthesis at the chain elongation step and binds to the 50S ribosomal subunit Net effect: bacteriostatic activity					
Azithromycin	GPC Atypical lung pathogens	Load: 500 mg × 1 Mtce: 250 mg q24 h IHD/CRRT: same	IV IV/PO	No	May have some activity against some Gram-negative organisms Prolongs QTc interval (rare); minimal to no CYP450 interactions
Sulfonamides MOA: individually block two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria Net effect: bacteriostatic activity					
Sulfamethoxazole/ trimethoprim	GPC GNB	5–20 mg TMP/kg per day, divided q6–12 h IHD: 2.5–10 mg TMP/kg q24 h CRRT: 2.5–7.5 mg TMP/kg q12 h	IV PO	Yes	No activity against group A *Streptococcus* Dose calculated based on trimethoprim component
Tetracyclines and glycylcycline MOA: binds to the 30S and possibly the 50S ribosomal subunits resulting in inhibited protein synthesis Net effect: bacteriostatic activity					
Doxycycline	GPC GNB (no PA) Anaerobes Atypicals	100 mg q12 h IHD/CRRT/PD: same	IV PO	No	Good tissue penetration with minimal CSF penetration Absorption interaction with di- or trivalent cations Covers mycoplasma, chlamydia, rickettsiae; resistance in Gram-negative aerobic organisms is very common
Tigecycline	GPC (MRSA, VRE, DRSP) GNB (no PA) Anaerobes Atypicals	Load: 100 mg MD: 50 mg q12 h IHD/CRRT: same	IV	No	Very broad spectrum except *Morganella morganii, Proteus mirabilis, Providencia* sp. and *P. aeruginosa* Not recommended for bloodstream infections due to high volumes of distribution and low serum concentrations Not recommended for hospital-acquired or ventilator-associated PNA

Polymyxins MOA: increase permeability of the bacterial cell membrane leading to death of the cell Net effect: bactericidal activity					
Polymyxin B	GNB (PA)	7500–12 500 units/kg q12 h	IV	Yes	Useful for multidrug-resistant *P. aeruginosa* and *A. baumannii* Renal dose adjustments may not be necessary according to recent literature
Colistin methanesulfate (polymyxin E)	GNB (PA)	Load: 270 mg MD: 135 mg q12 h IHD: 1.5 mg/kg q24–48 h CRRT: 2.5 mg/kg q48 h	IV	Yes	Useful for multidrug-resistant *P. aeruginosa* and *A. baumannii* Nebulization may be used as an adjuvant for VAP
Aminoglycosides MOA: binds to the 30S and possibly the 50S ribosomal subunits resulting in inhibited protein synthesis Net effect: bactericidal activity					
Amikacin	GNB (PA)	5–7.5 mg/kg q8 h or Extended interval: 15 mg/kg q24–48 h IHD: 5–7 mg/kg q48–72 h CRRT: load 10 mg/kg MD 7.5 mg/kg q12–24 h	IV	Yes	Use ideal body weight (IBW) for dosing. If actual weight (AW) is >125% of the IBW, use adjusted body weight (ABW): ABW = IBW + 0.4 × (AW – IBW) Conventional; target peak concentrations (after third dose): 26–40 mg/L: life-threatening 21–25 mg/L: serious infections 15–20 mg/L: UTI Trough concentration (prior to next dose) <5 mg/L IHD: redose when pre-HD concentration <10 mg/L or post-HD <6–8 mg/L CRRT: target peak concentration 15–30 mg/L; redose when concentration <10 mg/L Use ideal body weight (IBW) for dosing. If actual weight (AW) is >125% of the IBW, use adjusted body weight (ABW): ABW = IBW + 0.4 × (AW – IBW)

(*Continued*)

Table 45.2 (*Continued*)

Generic name	General spectrum of activity	Usual initial dosing for critically ill	Route of administration	Renal dose adjustments	Clinical pearls
Gentamicin Tobramycin	GNB (PA) GNB (PA)	1–1.7 mg/kg q8 h or Extended interval: 7 mg/kg q24–48 h IHD: load 2–3 mg/kg, then 1–2 mg/kg q48–72 h CRRT: load 2–3 mg/kg, then: UTI: 1 mg/kg q24–36 h Serious: 1–1.5 mg/kg q24–36 h Life-threatening: 1.5–2.5 mg/kg q24–48 h	IV IV	Yes Yes	Conventional; target peak concentrations (after third dose): 8–10 mg/L: life-threatening 6–8 mg/L: serious infections 4–6 mg/L: UTI Trough concentration (prior to next dose) <1 mg/L IHD: redose when pre-HD concentration <1–2 mg/L CRRT: redose based on severity and random concentration: <1 mg/L: UTI <1.5–2 mg/L: serious infection <3–5 mg/L: life-threatening infection
Glycopeptide MOA: binds to peptidoglycan precursors blocking glycopeptide polymerization resulting in inhibited cell wall synthesis Net effect: bactericidal activity					
Telavancin	GPC (MRSA, VRE, DRSP)	10 mg/kg q24 h	IV	Yes	
Vancomycin	GPC (MRSA, DRSP)	Load: 15–25 mg/kg or 25–30 mg/kg (severe infection) MD: 15–20 mg/kg q8–12 h (infuse 1 g over 1 hour to avoid 'red man syndrome') IHD: load 15–25 mg/kg, then 5–10 mg/kg post-HD CRRT: load 15–25 mg/kg	IV	Yes	Use actual body weight for dosing Target trough concentrations (prior to fourth doses): ≥10 mg/L: always optimal to prevent resistance 12–15 mg/L: less complicated infections (SSI, UTI) 15–20 mg/L: complicated infections (IE, CNS, OM, PNA) Dosing adjustment based on trough Nephrotoxicity and ototoxicity are rare without a concomitant offending agent
		Susp/caps: 125–250 mg q6 h	PO	No	For *C. difficile* treatment

Oxazolidinone MOA: binds to the 23S ribosomal RNA of the 50S subunit, thus inhibiting translation and protein synthesis Net effect: bacteriostatic activity					
Linezolid	GPC (MRSA, VRE)	600 mg q12 h IHD/CRRT: same	IV/PO	No	MAOI, interacts with catecholamines; lactic acidosis; myelosuppression; peripheral and optic neuropathy Not recommended for bloodstream infections
Tedizolid	GPC (MRSA)	200 mg q24 h	IV/PO	No	MAOI, interacts with catecholamines
Cyclic lipopeptide MOA: binds to bacterial cell membranes and causes causing a rapid depolarization of membrane potential thus inhibiting protein synthesis Net effect: bactericidal activity					
Daptomycin	GPC (MRSA, VRE)	6-8 mg/kg q24 h IHD: 4–6 mg/kg q48 h CRRT: 4–6 mg/kg q48–72 h PD: dose based on CrCl <30 mL/min	IV	Yes	Deactivated by surfactant in lungs, thus ineffective for PNA Monitor CPK weekly, consider stopping statins due to risk of myopathy; eosinophilic pneumonia (risk usually with >2–4 weeks of treatment)
Nitroimidazole MOA: penetrates cellular cytoplasm along with free radicals, inhibits DNA synthesis and interacts with DNA to cause DNA degradation thus inhibiting protein synthesis leading to death of the bacteria Net effect: bactericidal activity					
Metronidazole	Anaerobes	500 mg q6–8 h IHD: 500 mg q8–12 h CRRT: 500 mg q6–12 h PD: 500 mg q8–12 h	IV/PO	No	Disulfiram-like reaction with ethanol; peripheral, autonomic, and optic neuropathy (generally with high doses or prolonged treatment)

BLI, beta-lactamase inhibitor; BSA, body surface area; CNS, central nervous system; CPR, cardiopulmonary resuscitation; CrCl, creatinine clearance by Cockcroft-Gault equation; CRRT, continuous renal replacement therapy; CSF, cerebrospinal fluid; DRSP, drug-resistant *Streptococcus pneumoniae;* ESRD, end-stage renal disease; FDA, Food and Drug Administration (USA); GI, gastrointestinal; GNB, Gram-negative bacilli; GPC, Gram-positive cocci; IE, infectious endocarditis; IHD, intermittent hemodialysis; IM, intramuscular; IV, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; MAOI, monoamine oxidase inhibitor; MIC, minimum inhibitory concentration; MD, maintenance dosing; MOA, mode of action; MSSA, methicillin-sensitive *Staphylococcus aureus;* MRSA, methicillin-resistant *Staphylococcus aureus;* OM, osteomyelitis; PA, *Pseudomonas aeruginosa;* PNA, pneumonia; PO, oral (or enteral route); SSI, skin and soft tissue infection; TMP, trimethoprim; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci; VAP, ventilator-associated pneumonia. Consult a pharmacist for peritoneal dialysis dosing.

Extracorporeal membrane oxygenation

- Changes in pharmacokinetic parameters associated with ECMO result from sequestration of the drug, increase in distribution, changes in renal and hepatic blood flow, and flow rate from the system.
- The pharmacokinetic effects have been minimally studied and mostly reported as case series in neonates.
- Effects of ECMO seem to increase distribution of vancomycin, gentamicin, and cefoxitin. However, the extent of clearance appears unchanged.
- Individualized antimicrobial regimens and therapeutic drug monitoring of vancomycin and aminoglycosides should be employed.

Inhaled antibiotic therapy

- Current evidence suggests that the improved clinical outcomes with adjunctive inhaled antibiotic therapy in certain patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) outweigh the potential harms and increased costs.
- Consider inhaled colistin, tobramycin, or gentamicin in conjunction with systemic antibiotics in the treatment of patients with VAP due to gram-negative bacilli only susceptible to polymyxins or aminoglycosides
- Consider inhaled colistin in conjunction with systemic antibiotics in the treatment of patients with HAP and VAP due to:
  - *Acinetobacter* species only susceptible to polymyxins.
  - Carbapenem-resistant pathogens only susceptible to polymyxins.
- Adjunctive inhaled antibiotic therapy may also be considered as salvage therapy in VAP patients not responding to intravenous antibiotics alone, whether or not the pathogen is multidrug resistant.
- Current cystic fibrosis guidelines state that there is insufficient information to recommend for or against the continued use of inhaled antibiotics in patients with cystic fibrosis treated with the same antibiotics intravenously for the treatment of an acute exacerbation of pulmonary disease.

Treatment of resistant organisms

- There is an increasing incidence of infections due to multidrug-resistant (MDR) gram-positive cocci and gram-negative bacilli in critical care settings.
  - Gram-positive organisms: methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus*, vancomycin-resistant enterococci, and penicillin-resistant *Streptococcus pneumoniae*.
  - Increasingly encountered gram-negative-resistant organisms: extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae (e.g. *Klebsiella* species, *Escherichia coli*, and *Enterobacter* species), carbapenem-resistant Enterobacteriaceae (CRE), including those due to *Klebsiella pneumoniae* carbapenemase, and MDR *Pseudomonas aeruginosa* and *Acinetobacter* species.
- ESBL organisms:
  - Carbapenems are the treatment of choice. In patients with bacteremia due to these organisms, improved survival is seen with imipenem or meropenem. Although they test susceptible to cephamycins (e.g. cefoxitin, cefotetan), there are few data demonstrating efficacy.
  - Ceftolozane-tazobactam and ceftazidime-avibactam are newer beta-lactam/beta-lactamase inhibitors, which have activity against most ESBL-producing Enterobacteriaceae. Limited clinical data show promise.

- For serious infections due to CRE, combination therapy with two or more agents should be used. Generally a polymixin-based regimen (if susceptible) is given, plus other agents including:
  - Tigecycline, aztreonam, or an aminoglycoside such as gentamicin (based on susceptibility testing).
  - Ceftazidime-avibactam (limited clinical experience, used as an alternative agent as part of a combination regimen).
  - A carbapenem such as meropenem, as in vitro and animal studies have demonstrated synergistic killing.
- For MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa* infections, a polymixin-based regimen in combination with another agent should be used.

Gram-negative resistance due to beta-lactamase production

- Beta-lactamases are bacterial enzymes that inactivate beta-lactam antibiotics by hydrolyzing the beta-lactam ring.
- The Ambler classification system classifies beta-lactamases into four groups (A–D) based on their amino acid sequences.

Extended-spectrum beta-lactamases

- ESBLs are class A beta-lactamases that hydrolyze penicillins, most cephalosporins, and monobactams (aztreonam). They are inactive against the cephamycins (e.g. cefoxitin, cefotetan) and the carbapenems.
- Risk factors include the prior use of beta-lactam antibiotics, the presence of indwelling devices or previous invasive procedures, admission from a long-term care facility, and comorbidities.

Carbapenemases

- Carbapenemases hydrolyze carbapenems in addition to other beta-lactams.
- Bacteria with carbapenemases often have additional resistance mechanisms that confer resistance to most antibiotics. The most important carbapenemases are:
  - *Klebsiella pneumoniae* carbapenemase (KPC) – class A:
    - The most common carbapenemase in the USA.
    - Found in many Enterobacteriaceae and *Pseudomonas aeruginosa*.
  - New Delhi metallo-beta-lactamase (NDM-1) – class B:
    - The incidence is low but increasing.
    - NDM-1 is found in *Klebsiella* species, *E. coli*, other Enterobacteriaceae, and *Acinetobacter* species.
    - NDM-1 inactivates first to fourth generation cephalosporins and carbapenems but not aztreonam.
  - The OXA group – class D:
    - Another emerging carbapenemase.

Antimicrobial stewardship programs (ASP)

- Thirty to 60% of antibiotics given in ICUs are unnecessary, inappropriate, or suboptimal.
- The goal of an ASP is to optimize clinical outcome while minimizing unintended consequences of antimicrobial use.

- Core members of an ASP as defined by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America include an infectious disease (ID) physician, an ID clinical pharmacist, a clinical microbiologist, an information systems specialist, an infection control professional, and a hospital epidemiologist.
- Antimicrobial stewardship is important because it:
  - Improves patient outcomes.
  - Decreases the incidence of drug-resistant organisms.
  - Reduces the adverse effects of drug therapy.
  - Reduces costs.
- Antimicrobial stewardship is especially important in critical care because:
  - A large percentage of patients receive antimicrobials in critical care units.
  - There are many complicated and difficult to treat infections.
  - Clinicians may be more likely to start and less likely to discontinue antimicrobials, including broad spectrum antibiotics, in critically ill patients.
  - Patients may be more at risk of developing adverse effects from antimicrobials when critically ill.
- As part of critical care antimicrobial stewardship, clinicians should:
  - Diagnose and identify pathogens as early and rapidly as possible.
  - Initiate empiric regimens based on the most likely organism(s) to be causing a specific infection, local susceptibility patterns, previous antibiotic therapy, cost effectiveness, and the likelihood of resistance developing.
  - Ensure sufficient concentration of the antimicrobial at the site of the infection.
  - At 48–72 hours, reassess therapy.
  - Apply concepts of de-escalation: decrease the spectrum of the antimicrobial regimen by tailoring it to the site and susceptibility of the identified organisms. Stop therapy altogether if infection is deemed unlikely at the time of reassessment.
    - Stop vancomycin and linezolid if methicillin-resistant *Staphylococcus aureus* (MRSA) is not found unless the patient is allergic to beta-lactams or has an infection with gram-positive bacteria susceptible only to one of these agents.
    - Broad spectrum agents such as the carbapenems, piperacillin-tazobactam, and cefepime should be continued only if culture results yield organisms susceptible to these agents alone.
  - Convert medications as soon as possible from the intravenous to the enteral route. Antimicrobials such as fluoroquinolones, oxazolidinones (e.g. linezolid), clindamycin, trimethoprim-sulfamethoxazole, metronidazole, fluconazole, and voriconazole have high oral bioavailability.
  - Use the evidence-based duration of therapy for defined infections.
- Biomarkers may have a role in the decision to stop the antibiotic therapy of certain diseases.
  - Current guidelines recommend using procalcitonin levels plus clinical criteria rather than clinical criteria alone in the decision to discontinue antibiotics in patients with HAP and VAP.
  - Procalcitonin may be used to help determine the timing of discontinuation of antibiotics in the empiric treatment of sepsis in patients who subsequently show no evidence of infection.

Antifungal and antiviral therapy (Tables 45.1–45.4)

Table 45.3 Pharmacotherapy of most common antifungals for critical care.

Generic name	General spectrum of activity	Usual initial dosing for critically ill	Route of administration	Renal dose adjustments	Clinical pearls
Azoles MOA: interferes with fungal cytochrome P450 activity, decreasing ergosterol synthesis and therefore inhibiting cell membrane synthesis					
Fluconazole	Blastomycosis, candidiasis (not *Candida krusei, C. glabrata*), coccidioidomycosis, cryptococcosis	Load: 400–800 mg MD: 200–400 mg q24 h IHD: 200–400 mg q48–72 h or 100–200 mg q24 h CRRT: 200–800 mg q24 h	IV PO	Yes	Excellent oral bioavailability Moderate inhibitor of CYP 3A4, thus interacts with substrates
Isavuconazole	Aspergillosis, mucormycosis	Load: 200 mg q8 h × 6 doses MD: 200 mg q24 h	IV PO	No	
Itraconazole	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis	200–400 mg q24 h IHD/CRRT: 200 mg q12 h × 4, then 200 mg q24 h	PO	Yes	
Posaconazole	Aspergillosis, candidiasis, mucormycosis	Load: 300 mg q12 h, day 1 MD: 300 mg q24 h Tabs: 300 mg q12 h, day 1 MD: 300 mg q24 h Susp: 200 mg q6 h, day 1 400 mg q12 h with disease stabilization	IV PO PO	No	Capsules and oral suspension not interchangeable due to unpredictable absorption (consider monitoring serum concentrations) Strong CYP 3A4 inhibitor IV not recommended with CrCl <50 due to accumulation of SBECD, a toxic vehicle Strong CYP 3A4 inhibitor
Voriconazole	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis (no mucormycosis)	Load: 6 mg/kg q12 h, day 1 MD: 4 mg/kg q12 h Weight ≥40 kg: 200 mg q12 h Weight <40 kg: 100 mg q12 h IHD/CRRT: 400 mg q12 h × 2, then 200 mg q1 2h	IV PO PO	No	IV not recommended with CrCl <50, IHD, and CRRT due to accumulation of SBECD, a toxic vehicle Strong CYP 3A4 inhibitor Do not use for urinary tract infections Transient visual changes; hallucinations; photosensitivity; rash

(*Continued*)

Table 45.3 (*Continued*)

Generic name	General spectrum of activity	Usual initial dosing for critically ill	Route of administration	Renal dose adjustments	Clinical pearls
Echinocandins MOA: non-competitive inhibitor of 1,3-β-D-glycan synthase resulting in reduced formation of 1,3-β-D-glycan, essential for stability of the fungal cell wall					
Anidulafungin	Aspergillosis, candidiasis	Load: 100–200 mg × 1 ND: 50–100 mg q24 h IHD/CRRT: same	IV	No	Does not treat urine or CNS fungal infections
Caspofungin		Load: 70 mg × 1 MD: 50–70 mg q24 h IHD/CRRT/PD: same	IV	No	Does not treat urine or CNS fungal infections; hepatic dose adjustment recommended to maintenance of 35 mg q24 h
Micafungin		50–150 mg q24 h IHD/CRRT/PD: same	IV	No	
Polyenes MOA: binds to ergosterol, altering cell membrane permeability causing leakage of cell components with subsequent cellular death					
Amphotericin B deoxycholate	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis	0.3–1 mg/kg q24 h Max: 1.5 mg/kg q24 h IHD/CRRT: same	IV	No	Infuse over 4–6 hours to prevent infusion-related adverse effects (nausea, vomiting, fever, rigors); may cause nephrotoxicity, electrolyte imbalance
Amphotericin B lipid complex		5 mg/kg q24 h IHD/CRRT/PD: same	IV	No	Infuse over 2 hours; risk of nephrotoxicity is less than amphotericin B deoxycholate; do not use an in-line filter
Liposomal amphotericin B		3–6 mg/kg q24 h IHD/CRRT/PD: same	IV	No	Infuse over 2 hours using a 1.0 micron in-line filter; risk of nephrotoxicity is less than amphotericin B deoxycholate; infusion-related adverse effects may include chest pain, dyspnea, hypoxia, abdominal pain, urticaria

CNS, central nervous system; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; IV, intravenous; MD, maintenance dosing; MOA, mode of action; PD, peritoneal dialysis; PO, oral (or enteral route); SBECD, sulfobutylether-β-cyclodextrin.

Table 45.4 Pharmacotherapy of most common antivirals for critical care.

Generic name	General spectrum of activity	Usual initial dosing for critically ill	Route of administration	Renal dose adjustments	Clinical pearls
Acyclovir	HSV type 1, 2 VZV	5–10 mg/kg q8 h IHD: 2.5–5 mg/kg q24 h CRRT: 5–10 mg/kg q12–24 h	IV IV	Yes	Nephrotoxicity with IV administration may be prevented with adequate hydration
		200–800 mg 5 × daily	PO		
Ganciclovir	CMV	Initial: 5 mg/kg q12 h IHD: 1.25 mg/kg q48–72 h, then 0.625 mg/kg q48–72 h CRRT: CVVH: 2.5 mg/kg q24 h, then 1.25 mg/kg q24 h CVVHD/CVVHDF: 2.5 mg/kg q12 h, then q24 h	IV	Yes	Infusion over 1 hour; monitor for myelosuppression
Valacyclovir	HSV VZV	500 mg–2 g q12–24 h (2 g q12 h × 1 day for oral HSV)	PO	Yes	Prodrug: converted to acyclovir; risk of TTP/HUS in immunocompromised patients receiving 8 g/day
Valganciclovir	CMV	Initial: 900 mg q12 h MD: 900 mg q24 h	PO	Yes	Prodrug: converted to ganciclovir

CMV, cytomegalovirus; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; HSV, herpes simplex virus; IHD, intermittent hemodialysis; IV, intravenous; MD, maintenance dosing; PD, peritoneal dialysis; PO, oral (or enteral route); TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; VZV, varicella-zoster virus.

Reading list

Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy 2009;29(5):562–77.

Kaki R, et al. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother 2011;66:1223–30.

Mehrad B, et al. Antimicrobial resistance in hospital-acquired gram-negative bacterial infections. Chest 2015;147(5):1413–21.

Nicolau DP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39(3):650–5.

Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. Clin Infect Dis 2004;38:864–70.

Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37(3):840–51.

Vincent JL, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302(21):2323–9.

Guidelines

National society guidelines

Title	Source	Date and reference
Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines	Infectious Diseases Society of America and the American Thoracic Society	2016 Clin Infect Dis 2016;63:e61–111
Implementing an Antibiotic Stewardship Program	Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America	2016 Clin Infect Dis 2016;62(10):e51–77
Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update	Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)	2018 Clin Infect Dis 2018;66(7):e1–48
Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update	Infectious Diseases Society of America	2011 Clin Infect Dis 2011;52(4):e56–93
Therapeutic Monitoring of Vancomycin in Adult Patients: A Consensus Review	American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists	2009 Am J Health-Syst Pharm 2009;66:82–98
Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update	Infectious Diseases Society of America	2014 Clin Infect Dis 2014;59(2):e10–52

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

with website

CHAPTER 46

Pneumonia

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OVERALL BOTTOM LINE

- Pneumonia is the leading infectious cause of hospitalization and death among adults, with mortality exceeding 35% for those requiring ICU admission.
- Initiation of early and appropriate antibiotic therapy in patients with severe pneumonia is associated with increased survival.
- When choosing antibiotics, history of recent antibiotic use, risk factors for multidrug-resistant (MDR) pathogens, and the local antibiogram should be considered.
- Scoring systems for severe pneumonia are underutilized and may be useful in assessing the severity of illness in community-acquired pneumonia (CAP).
- Delay in ICU admission for patients with severe pneumonia is associated with increased mortality.

Background

Definition

- Pneumonia is an infection of the lower respiratory tract due to bacteria, viruses, or less commonly fungal organisms.
- Disease severity ranges from mild outpatient illness to severe infection with respiratory failure and sepsis, requiring admission to the ICU.

Disease classification

- Community-acquired pneumonia (CAP) is an acute infection of the lower respiratory tract acquired in the community, without hospitalization or regular exposure to health care facilities. Severe CAP is defined as requiring ICU management for shock, organ dysfunction, or mechanical ventilation.
- Nosocomial pneumonia can be subdivided into hospital-acquired pneumonia (HAP), pneumonia that develops after 48 hours of hospitalization, and health care-associated pneumonia (HCAP). It occurs in patients with extensive health care contact and at risk for multidrug-resistant (MDR) pathogens. Risks for HCAP include recent hospitalization >2 days in the past 90 days, contact with health care facilities (e.g. nursing home residence, hemodialysis center), recent antibiotic use, home wound care or infusion therapy, immunosuppression (e.g. corticosteroid use), or structural lung disease (e.g. bronchiectasis).
- Ventilator-associated pneumonia (VAP) is a type of HAP that develops after 48 hours of invasive mechanical ventilation. In 2013, the US Center for Disease Control and Prevention (CDC) recognized that the definition of VAP was neither sensitive nor specific. The CDC introduced the new concept of ventilator-associated events (VAEs), a tiered surveillance definition. See also Chapter 44.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

- Ventilator-associated condition (VAC): worsening oxygenation (increase in FiO_2 ≥0.2 or PEEP ≥3 cmH_2O) for ≥2 days following a period of stability.
- Infection-related ventilator-associated complication (IVAC): VAC with fever or hypothermia, and/or leukocytosis or leukopenia, and receiving new antibiotics for ≥4 days.
- Possible VAP: IVAC with purulent respiratory secretions with Gram stain evidence of respiratory infection or growth of a pathogen from respiratory cultures.
- Probable VAP: Gram stain evidence of infection plus significant growth of a pathogenic organism from endotracheal aspirate, bronchoalveolar lavage (BAL), protected brush specimen, pleural fluid, or lung tissue; or detection of respiratory viruses or *Legionella* species.

Incidence/prevalence

- The World Health Organization (WHO) estimates that lower respiratory tract infection is the most common infectious cause of death in the world, with almost 3.5 million deaths annually.
- In the USA, the annual incidence of CAP requiring hospitalization is 25 cases per 10 000 adults, with the highest rates among those aged 65–79 years (nine times higher) and in those 80 years or older (25 times higher) as compared with those under 50 years of age.
- HAP is the second most common nosocomial infection with a rate of 5–10 cases per 1000 adult patients.

Etiology

- Varies with the season and is dependent on the patient's risk factors (see later in this chapter) and the setting in which pneumonia develops.
- In a large study by the CDC, causative agents for CAP were found in only 38% of patients, with viruses detected in 27% and bacteria in 14% of patients.
- Human rhinovirus and influenza are the most common viral pathogens isolated, followed by human metapneumovirus, respiratory syncytial virus, parainfluenza virus, coronavirus, and adenovirus.
- *Streptococcus pneumoniae* is the most common bacterial cause of CAP, followed by *Hemophilus influenza*, and atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*,and *Legionella*.
- In patients with severe CAP, *S. pneumoniae* is most common, but *Legionella*, gram-negative bacilli, *Staphylococcus aureus*, and influenza are important considerations.
- Causes of nosocomial pneumonia tend to be more bacterial in nature, including methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcal* spp., resistant gram-negative organisms (*Pseudomonas aeruginosa, Acinetobacter, Klebsiella, Enterobacter, Stenotrophomonas* and *Escherichia coli*). Anaerobic pathogens have a minor role.
- Viral and fungal pathogens should be considered in immunocompromised hosts. *Pneumocystis jirovecii* can cause pneumocystis pneumonia (PCP) in patients with acquired immune deficiency syndrome (AIDS) and those taking chronic corticosteroids.

Pathology/pathogenesis

- Pneumonia develops when host defenses are overwhelmed by an infectious pathogen. This is typically a result of an inadequate immune response, often due to underlying comorbidities, immunosuppression, or from anatomic abnormalities (e.g. endobronchial obstruction, bronchiectasis). Pneumonia also occurs when the host defense system is overwhelmed by a large inoculum of microorganisms (e.g. massive aspiration) or a particularly virulent organism.
- The primary route of infection is by micro-aspiration of oropharyngeal pathogens. Hospitalized patients become colonized with nosocomial organisms in as little as 48 hours. Thus, patients with impaired mentation (e.g. stroke, dementia, intoxication) are particularly at risk. Chronically ill patients may be colonized by pathogens, particularly gram-negative bacteria, and develop pneumonia when the immune response is inadequate.

- Other routes of entry include inhalation (viruses, *Legionella*, and *Mycobacterium tuberculosis*), hematogenous dissemination from extrapulmonary sites of infection (right-sided endocarditis), and direct extension.
- In mechanically ventilated patients, aspiration of oropharyngeal and gastrointestinal contents can lead to pneumonia. Additionally, water reservoirs and respiratory devices can serve as a source of pneumonia.

Predictive/risk factors for CAP

Risk factor	
Advanced age	HIV and AIDS
Alcohol abuse	History of pneumonia
Asplenia	Immobility
Cerebrovascular disease, stroke, and dementia	Lung cancer
Chronic cardiovascular disease	Male sex
Chronic liver or kidney disease	Malignancy
Chronic lung disease (COPD, asthma)	Malnutrition
Cigarette smoking	Poor dental hygiene
Diabetes mellitus	Swallowing difficulty

Risk factors for specific pathogens that cause pneumonia

Organism	Risk factor
Penicillin-resistant and drug-resistant *S. pneumoniae*	Age >65 years Alcoholism Immune suppression Multiple medical comorbid conditions Beta-lactam therapy within past 3 months Exposure to a child in daycare center
Enteric gram-negative bacteria	Recent antibiotic therapy Residence in a nursing home Underlying cardiopulmonary disease Multiple medical comorbid conditions
Pseudomonas aeruginosa	Malnutrition Structural lung disease (bronchiectasis) Corticosteroid therapy (prednisone >10 mg/day) Broad spectrum antibiotic therapy for >7 days in the past month

Prevention

BOTTOM LINE

- Follow recommended guidelines for pneumococcal and influenza vaccination.
- Smoking cessation and abstinence from alcohol can reduce the risk of pneumonia and progression to severe pneumonia.
- Utilization of ventilator bundles reduces the incidence of VAP.
- Standard infection control practices prevent cross contamination.

Screening

- There are no screening tools for pneumonia.
- Identifying patients at risk for MDR pathogens is important for infection control.

Primary prevention

- Smoking cessation and abstinence from alcohol abuse can reduce the risk of pneumonia.
- All individuals over the age of 65 years, and high risk persons should receive pneumococcal (PCV-13 and PCV-23) and annual influenza vaccination.
- All patients hospitalized with a medical illness should be considered for pneumococcal and influenza vaccination.
- Strategies to prevent nosocomial pneumonia include use of non-invasive positive pressure ventilation (NPPV) when possible.
- Preventive strategies for VAP are combined in ventilator bundles: limit sedation, daily interruption of sedation, daily ventilator weaning trials, early mobilization, head of the bed elevation >30°, and oral care with chlorhexidine.
- Use of endotracheal tubes (ETTs) with subglottic secretion drainage ports can potentially reduce VAP, however this is not in widespread practice.
- Change ventilator tubing only when visibly soiled.
- Selective oral or digestive decontamination, silver coated ETT, and early tracheostomy remain controversial in preventing VAP.

Secondary prevention

- Vaccination and cessation of tobacco and alcohol abuse.
- Antibiotic stewardship programs and infection control measures, especially proper hand hygiene, prevent the emergence of MDR bacteria.

Diagnosis

BOTTOM LINE

- Pneumonia is a clinical diagnosis comprising productive cough, fever, dyspnea, or pleuritic chest pain.
- Laboratory findings may include leukocytosis or leukopenia and hypoxemia.
- Radiologic evidence of pneumonia may not be evident at the time of clinical presentation.
- VAEs require deterioration in oxygenation (VAC) with change in temperature, WBC count, purulent secretions, and microbiologic evidence of infection.

Differential diagnosis

Differential diagnosis	Features
Pulmonary edema	Known or previously undiagnosed cardiac disease. Patients present with weight gain, lower extremity edema, and orthopnea. Examination reveals basilar rales, cardiac gallop, jugular venous distension, and edema. Chest radiograph often shows airspace opacities and brain natriuretic peptide may be elevated
Aspiration pneumonitis	History of neurologic disease, sedative use, or vomiting. Clinical signs of pneumonia can be delayed up to 2–3 days following aspiration event
Post-obstructive pneumonia	History of pulmonary malignancy, weight loss, or aspiration of foreign body. Exam may reveal unilateral wheezing. Chest radiograph can show mass-like consolidation, atelectasis, or unresolving pneumonia

Differential diagnosis	Features
Pulmonary infarct	Acute presentation with dyspnea, pleurisy, and hemoptysis. Chest radiographs can show wedge-shaped opacities or sharp cutoffs of pulmonary vessels and CT angiogram confirms pulmonary embolism
Acute exacerbation of chronic lung disease (COPD, bronchiectasis, fibrosis)	Acute dyspnea, wheezing, and/or productive cough. Examination and imaging can mimic pneumonia
Acute respiratory distress syndrome	Acute dyspnea secondary to lung injury from pulmonary or non-pulmonary insult. Hypoxemia and crackles often present. Chest imaging shows acute, bilateral alveolar–interstitial opacities
Cryptogenic organizing pneumonia	Recurrent pneumonia with fleeting opacities. Tissue diagnosis and prompt initiation of corticosteroid therapy are needed
Acute eosinophilic pneumonia	Presents like typical pneumonia, however does not resolve with antibiotics. Chest imaging may show peripheral opacities and BAL shows eosinophil-predominant cell count. Lung biopsy confirms diagnosis
Idiopathic interstitial pneumonia	Interstitial lung disease that can present like pneumonia with abnormal chest imaging. Lung biopsy often needed for diagnosis
Lung disease associated with connective tissue disease	History of autoimmune disease and may present with additional, non-pulmonary findings. Chest imaging reveals interstitial or nodular opacities
Drug-induced pulmonary toxicity	Use of medications known to cause pulmonary toxicity (e.g. methotrexate, nitrofurantoin, amiodarone). Chest imaging can show interstitial changes or ground glass opacities

Typical presentation

- Patients present with fever, cough with productive sputum, and dyspnea. Cough and fever are present in 80% of patients with pneumonia. Purulent sputum is commonly seen in bacterial pneumonia while watery sputum is often associated with atypical organisms. Pleurisy may be present and can be indicative of severe disease or parapneumonic effusion (PPE).
- Non-respiratory symptoms such as confusion or generalized weakness may be the initial presentation in the elderly.
- Patients with *Legionella* pneumonia can present with confusion, diarrhea, and electrolyte abnormalities.
- In patients undergoing mechanical ventilation for >48 hours, the diagnosis of VAE/VAP should be considered (see Definitions section).

Clinical diagnosis

History

- Pneumonia can present in a subacute or acute manner, with symptoms such as cough, purulent or blood-tinged sputum, dyspnea, pleurisy, fever, and chills.
- Extrapulmonary symptoms such as confusion or diarrhea may be present.
- Special attention should be paid to recent travel history and exposure to sick contacts. It is crucial to identify MDR risk factors such as alcoholism, malnutrition, immunosuppression, recent antibiotic use, exposure to children in day care or health care facilities, and medical comorbidities.
- Duration of hospitalization or ventilator support guides the choice of antibiotics.

Physical examination

- Abnormal vital signs include fever, hypothermia, tachycardia, tachypnea, and hypoxemia.
- Crackles are auscultated over the involved lobes. Bronchial breath sounds, tactile fremitus, whispered pectoriloquy, and egophony are findings of consolidation.
- Patients with pleural effusion have decreased tactile fremitus and dullness to percussion.

Useful clinical decision rules and calculators

- Scoring systems are infrequently used in clinical practice but were designed to predict the severity of CAP and determine the optimal site of care.
- The 2007 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) consensus guidelines recommend using the CURB-65 score or pneumonia severity index (PSI) to guide the initial site of treatment for adults with CAP.
  - A person with a CURB-65 score of 2 should be hospitalized and those with a score of ≥3 should be assessed for ICU admission. See http://www.mdcalc.com/curb-65-severity-score-community-acquired-pneumonia/.
  - The PSI risk class correlates directly with mortality rate. See http://www.mdcalc.com/psi-port-score-pneumonia-severity-index-adult-cap/.

ATS/IDSA criteria for ICU admission for CAP

Major criteria (1 or more = ICU admit)	**Minor criteria (3 or more = ICU admit)**
Endotracheal intubation and mechanical ventilation	Respiratory rate ≥30/min or PaO_2/FiO_2 ratio ≤250
Shock requiring vasopressors	Multilobar infiltrates
	Confusion or delirium
	Blood urea nitrogen (BUN) ≥20 mg/dL
	Leukopenia (WBC count 4000/mm^3)
	Thrombocytopenia (platelet count <100 000/mm^3)
	Hypothermia (core temperature <36°C)
	Hypotension requiring aggressive fluid resuscitation

Laboratory diagnosis

List of diagnostic tests

- Basic laboratory testing includes: complete blood count (CBC), basic metabolic panel (BMP), lactic acid, and arterial blood gas (ABG).
- Respiratory cultures can include sputum, tracheal aspirates, and samples obtained via bronchoscopy. Bronchoscopy may provide diagnostic value in patients unable to expectorate or those with treatment failure.
- Blood cultures are positive in <15% of cases (*S. pneumoniae* most commonly isolated) and are standard tests for patients with sepsis.
- Nasal swabs for viral infection during appropriate seasons, including rapid influenza assay and PCR.
- Urinary antigens for *Legionella* and *S. pneumoniae*.
- Procalcitonin is a biomarker used to support the diagnosis of bacterial pneumonia and guide antimicrobial therapy. Some algorithms call for withholding or discontinuing antibiotic therapy for levels <0.1 μg/L while administering antibiotics if >0.25 μg/L. Utilization is not yet widely accepted.
- C-reactive protein is elevated in bacterial pneumonia.

List of imaging techniques (Figures 46.1 and 46.2)

- Chest radiograph is the initial imaging method, but opacities may lag 2–3 days behind clinical symptoms.
- CT chest is used when the chest radiograph does not provide a clear cause of symptoms or if other pathologies (such as pulmonary embolism) are considered.
- Thoracic ultrasound is being increasingly used to detect pleuroparenchymal abnormalities.

Potential pitfalls/common errors made regarding diagnosis of disease

- Delay in diagnosis and in administration of appropriate antibiotics is associated with worse outcomes.
- Delayed ICU admission is associated with increased mortality.
- Elderly patients may not present with typical signs and symptoms.
- Diagnostic yield of respiratory cultures is low (<40%).
- Parapneumonic effusions may develop in up to 25% of patients and should be drained when feasible.
- In complicated or unresolving pneumonias, further imaging such as CT chest and thoracic ultrasound can evaluate for complications and alternative diagnoses.
- Resolution of pulmonary opacities may take 4–6 weeks. Follow-up imaging is indicated in patients with persistent symptoms and those at high risk for lung cancer.

Treatment

Treatment rationale

- Antibiotics are the mainstay of therapy.
- Differentiate between CAP and HAP/HCAP as the pathogenic organisms and therapies are different.
- ICU admission for high risk patients has been shown to reduce mortality.
- A trial of NPPV may be instituted in select ICU patients with pneumonia, however copious secretions and impaired cognition are contraindications.
- Invasive mechanical ventilation remains the standard ventilatory support for patients with severe pneumonia and acute respiratory failure.

When to hospitalize

- Clinical evaluation of vital signs, examination, and laboratory data.
- Although often not utilized, scoring systems may be used for triage decisions for CAP:
  - CURB-65: 2 points – hospitalization; 4–5 points – ICU admission.
  - ATS/IDSA: 1 major criteria or 3 minor criteria – ICU admission.

Managing the hospitalized patient

- Monitor for clinical improvement by assessing symptoms, fever curve, WBC count, oxygen saturation, and lactic acid levels.
- If there is no improvement despite 48 hours of appropriate antibiotics, consider parapneumonic effusion, other infectious etiology, and broadening antibiotics.

Principles of antimicrobial therapy

- Early and appropriate antibiotics are of utmost importance.
- Close attention to the patient's clinical status and need for ventilatory support.
- Choice of antibiotics should be based on type of pneumonia, site of care (ICU versus non-ICU), risks for MDR organisms, and local antibiogram.
- Hospitalized patients are treated with empiric parenteral antibiotic therapy.
- Switch from intravenous to oral antibiotic regimen can be considered based on clinical improvement.
- Treatment regimens may be simplified when the pathogen has been identified by reliable microbiologic testing.
- Duration of antibiotic therapy is based on type of pneumonia and patient's clinical response.
- CAP: 5–7 days for uncomplicated cases but severe cases may require longer courses. Assess for clinical stability for 48–72 hours before discontinuing antibiotics.
- HAP/HCAP: 7–8 days of empiric or culture-directed antibiotics (see Chapter 44).

- VAP: broad spectrum antibiotics for 72 hours, and then de-escalation based on culture data and clinical response.
- De-escalation of antibiotics and shorter courses have been shown to improve outcomes.
- Longer courses should be reserved for patients with delayed clinical response or those with *Pseudomonas, Acinetobacter, S. aureus*, or *Legionella* pneumonia.
- *Legionella* pneumonia requires 10–14 days of therapy; up to 21 days in the immunosuppressed. Although macrolides and respiratory fluoroquinolones are both effective, more rapid defervescence, fewer complications, and shorter hospital stay are seen with fluoroquinolone therapy.
- Procalcitonin-guided algorithms may be effective in safely reducing the duration of antibiotics for CAP. However point-of-care testing is not available at all institutions.
- Adjunctive aerosolized antibiotics can achieve higher concentrations in the lung than certain systemic antibiotics. Aerosolized antibiotics such as tobramycin, amikacin, and colistin have been used in VAP patients who are not responding despite appropriate systemic therapy or are infected with highly resistant organisms.
- Failure to respond to initial antibiotic therapy should prompt consideration for broader antibiotic coverage, antifungal therapy, or additional imaging.

Table of treatment

Treatment	Comments

Medical
CAP – inpatient, non-ICU
• Fluoroquinolone:
  ◦ Moxifloxacin 400 mg daily, levofloxacin 750 mg daily
Or
• Antipneumococcal beta-lactam *plus* macrolide or tetracycline:
  ◦ Ceftriaxone 1–2 g daily, cefotaxime 1–2 g daily, or ampicillin-sulbactam 1.5–3 g q6 h
  Plus
  ◦ Azithromycin 500 mg daily, clarithromycin 500 mg
q12 h, or doxycycline 100 mg q12 h
 	
Severe CAP – ICU
• Third-generation cephalosporin *plus* macrolide (preferred) or tetracycline (alternative):
  ◦ Ceftriaxone 2 g daily plus azithromycin 500 mg daily (preferred) or doxycycline 100 mg q12 h
Or
• Third-generation cephalosporin *plus* respiratory fluoroquinolone:
  ◦ Ceftriaxone 2 g daily plus either levofloxacin 750 mg or moxifloxacin 400 mg daily
• Influenza:
  ◦ Oseltamivir 75 mg twice a day × 5 days
• *Legionella*:
  ◦ Levofloxacin 750 mg or moxifloxacin 400 mg daily
  ◦ Azithromycin 500 mg daily
• Corticosteroids (controversial):
  ◦ Methylprednisolone 0.5 mg/kg q12 h × 5 days or prednisone 50 mg daily × 7 days
	Choice of antibiotics should be individualized and based on local antibiogram
	Narrow antibiotics based on culture and susceptibility data
	Monotherapy with respiratory fluoroquinolone is sufficient in non-severe CAP
	Cover atypical organisms with fluoroquinolone, macrolide, or tetracycline
	Combination therapy with macrolides shown to decrease mortality in CAP
	Doxycycline can be alternative to macrolide if QTc interval is prolonged.
	Dual therapy superior to monotherapy in critically ill patients with severe CAP and shock

Treatment	Comments
HCAP/VAP	
• Anti-MRSA: ◦ Vancomycin 15 mg/kg IV q12 h ◦ Linezolid 600 mg IV q12 h	MRSA pneumonia should be considered in influenza cases Linezolid shown to have less treatment failure in MRSA pneumonia
• Antipseudomonal, gram-negative pathogens: ◦ Beta-lactam: piperacillin-tazobactam 4.5 g q6 h ◦ Cephalosporins: cefepime 1–2 g IV q8–12 h or ceftazidime 2 g IV q8 h ◦ Carbapenem: imipenem 500 mg IV q6 h or 1 g q8 h, or meropenem 1 g IV qh ◦ Aminoglycoside: gentamicin or tobramycin 7 mg/kg/day IV, amikacin 20 mg/kg/day ◦ Fluoroquinolone: ciprofloxacin 400 mg q8 h or levofloxacin 750 mg daily	Aminoglycoside penetration into the lung and pleura is suboptimal; close monitoring of levels are essential Aerosolized antibiotics can be considered for resistant organisms
Surgical	
• Chest-tube drainage • VATS/thoracotomy • Bronchoscopy • Airway stenting	Multidisciplinary management to determine chest tube versus surgical management of complicated PPE and empyema Bronchoscopy can be diagnostic and therapeutic for endobronchial obstruction by foreign body Stenting of mainstem bronchi can relieve obstruction in setting of malignancy and post-obstructive pneumonia
Radiologic	
• Interventional radiology • Radiation-oncology	Fluoroscopic, ultrasound, or CT-guided drainage in appropriate cases Radiation therapy can be considered for malignancy-related endobronchial obstruction

Adjunctive therapy

- The use of adjunctive corticosteroids for CAP is currently controversial. Several studies have suggested improved clinical outcomes such as reductions in time to clinical stability, duration of illness, treatment failure, progression to ARDS, and need for mechanical ventilation. Further studies are needed before corticosteroids can be strongly recommended.
- Further imaging is indicated to assess for complications of pneumonia such as lung necrosis, abscess formation, complicated parapneumonic effusion, or empyema.
  - Pleural effusions associated with pneumonia should be sampled and drained.
  - Complicated PPEs and empyemas can be drained via tube thoracostomy with use of intrapleural tissue plasminogen activator (tPA) and DNase, or decorticated via video-assisted thoracoscopy surgery (VATS) or thoracotomy.

Prevention/management of complications

- Complications of pneumonia such as complicated PPE, empyema, lung necrosis, or abscess formation may develop.
- Chest tube drainage or thoracic surgical intervention may be necessary for complicated pleuropulmonary infection.
- Severe sepsis develops in almost 50% of patients with CAP; septic shock may be seen in 5% of CAP patients.
- CAP is the most common cause of ARDS. Lung protective ventilation can prevent the development of ARDS.
- Ventilator bundles have been shown to reduce VAP.

CLINICAL PEARLS

- Early, appropriate, and empiric antibiotics are the cornerstone of therapy.
- Appropriate ICU admission is needed for supportive therapies and monitoring.
- Ultrasound is emerging as a valuable tool for the diagnosis of pneumonia and monitoring for complications.
- Antibiotics stewardship programs are important to prevent the emergence of MDR organisms.

Special populations

Pregnancy

- Doxycycline and corticosteroid therapy should be avoided.

Children

- In severe disease, ribavirin therapy should be considered for respiratory syncytial virus or parainfluenza, as well as cidofovir for adenovirus.

Elderly

- The elderly are at higher risk for developing pneumonia and having a more severe disease course.

Others

- In HIV-positive and immunosuppressed patients, organisms such as *Pneumocystis jirovecii*, tuberculosis and non-tuberculosis mycobacteria, fungal organisms, nocardia, and actinomyces should be considered in addition to bacterial and viral organisms.

Clinical associations with specific populations/conditions

Condition	Commonly encountered pathogens
Alcoholism	*Streptococcus pneumoniae* (including penicillin resistant), anaerobes, gram-negative bacilli (*Klebsiella pneumoniae*), tuberculosis
Bat exposure	*Histoplasma capsulatum*
Bird exposure	*Chlamydia psittaci, Cryptococcus neoformans, H. capsulatum*
COPD/current or former smoker	*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*
Exposure to children in day care	Drug-resistant *S. pneumoniae*
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Poor dental hygiene	Anaerobes
Post-influenza pneumonia	*S. pneumoniae, Staphylococcus aureus* (including community-acquired MRSA), *H. influenzae*
Rabbit exposure	*Francisella tularensis*
Residence in nursing home	*S. pneumoniae*, gram-negative bacilli, *H. influenzae, S. aureus, Chlamydia pneumoniae,* anerobes; consider *Mycobacterium tuberculosis*
Sickle cell disease, asplenia	*S. pneumoniae*, *H. influenzae*
Structural disease of lung (e.g. bronchiectasis, cystic fibrosis)	*Pseudomonas aeruginosa* (mucoid), *Pseudomonas cepacia,* or *S. aureus* and MRSA, *Burkholderia cepacia, Stenotrophomonas maltophilia, H. influenza,* non-tuberculous *Mycobacterium* sp., *Aspergillus* sp.

(*Continued*)

Condition	Commonly encountered pathogens
Suspected bioterrorism	Anthrax, tularemia, plague
Travel to Asia	Severe acute respiratory syndrome (SARS), tuberculosis, melioidosis
Travel to Arabian Peninsula	Middle Eastern respiratory syndrome coronavirus (MERS-CoV)
Travel to/inhabiting regions bordering the Mississippi and Ohio River valleys	*Blastomyces dermatitidis*
Travel to southwestern USA	*Coccidioidomycosis*; hantavirus in selected areas

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Mortality in CAP remains high but improves with therapy.
- HCAP carries a higher mortality.

Prognosis for treated patients

- Mortality for CAP with treatment is 10%, 20% for HCAP.

Follow-up tests and monitoring

- Follow-up imaging should be obtained 4–6 weeks after pneumonia episode to assess for resolution.

Reading list

Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med 2014;371:1619–28.

Nair GB, Niederman MS. Pneumonia: considerations for the critically ill. In: Parillo JE, Dellinger RP (eds), Critical Care Medicine: Principles of Diagnosis and Management, 4th edition. Philadelphia: Elsevier Saunders, 2014.

Nair GB, Niederman MS. Ventilator-associated pneumonia: present understanding and ongoing debates. Intensive Care Med 2015;41(1):34–48.

Prina E, et al. Community acquired pneumonia. Lancet 2015;386:1097-108.

Wunderink R, et al. Community-acquired pneumonia. N Engl J Med 2014;370:543–51.

Suggested websites

www.cdc.gov/pneumococcal/clinicians/diagnosis-medical-mgmt.html

Guidelines

National society guidelines

Title	Source	Date and reference
Guidelines on the Management of Community-acquired Pneumonia in Adults	American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA)	2007 Mandell LA, et al. Clin Infect Dis 2007;44(Suppl 2):S27–72
Diagnosis and Treatment of Adults with Community-acquired Pneumonia	ATS/IDSA	2019 Metlay JP, et al. Am J Respir Crit Care Med 2019;200:809–21

(*Continued*)

(*Continued*)

Title	Source	Date and reference
Guidelines for the Management of Adults with HAP, HCAP and VAP	ATS/IDSA	2005 Niederman MS, et al. Am J Respir Crit Care Med 2005;171:388–416
Strategies to Prevent VAP in Acute Care Hospitals: 2014 Update	Society for Healthcare Epidemiology of America/IDSA	2014 Klompas M, et al. Infect Control Hosp Epidemiol 2014;35(8):915–36

International society guidelines

Title	Source	Date and reference/weblink
BTS Guidelines for the Management of CAP in Adults (2009) Summary of Recommendations	British Thoracic Society	2015 https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/community-acquired-pneumonia-in-adults-guideline/ Thorax 2009;64(Suppl III):iii1–55
Pneumonia in Adults: Diagnosis and Management	National Institute for Health and Care Excellence (NICE Guideline)	2014 www.nice.org.uk/guidance/cg191
Guidelines for the Management of Adult Lower Respiratory Tract Infections	European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID)	2011 Woodhead M, et al. Clin Microbiol Infect 2011;17(Suppl 6):E1–59
Defining, Treating and Preventing HAP	European Society of Intensive Care Medicine (ESICM), ERS, and ESCMID	2009 Torres A, et al. Intensive Care Med 2009;35:9–29

Evidence

Type of evidence	Title and comment	Date and reference
Epidemiological study	*Community-Acquired Pneumonia Requiring Hospitalization Among US Adults* Epidemiology of CAP and diagnostic yield of current pathogen detection	2015 Jain S, et al. N Engl J Med 2015;373:415–27
RCT	*Antibiotic Treatment Strategies for Community-acquired Pneumonia in Adults* In non-ICU patients with CAP, beta-lactam monotherapy may be non-inferior to beta-lactam plus macrolide combination or fluoroquinolone monotherapy with regard to 90 day mortality	2015 Potsma DF, et al. New Engl J Med 2015;372:1312–23
RCT	*Adjunct Prednisone Therapy for Patients with Community-Acquired Pneumonia: a Multicenter, Double-Blind Randomized, Placebo-Controlled Trial* Prednisone in CAP may shorten time to clinical improvement without significant complications	2015 Blum CA, et al. Lancet 2015;385:1511–18
RCT	*Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response: A Randomized Clinical Trial* Patients with severe CAP and elevated CRP had less treatment failure in methylprednisolone group	2015 Torres A, et al. JAMA 2015;313:677–86

(*Continued*)

Type of evidence	Title and comment	Date and reference
RCT	*Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection (MIST II)* Combination of tPA and DNase improved pleural fluid drainage and reduced need for surgical intervention	2011 Rahman N, et al. New Engl J Med 2011;365:518–26
RCT	*Procalcitonin Guidance of Antibiotic Therapy in Community Acquired Pneumonia: A Randomized Controlled Trial* Procalcitonin-guided antibiotic use decreased antibiotic exposure and duration without any adverse outcome	2006 Christ Cain M, et al. Am J Respir Crit Care Med 2006;174:84–93
RCT	*Comparison of 8 vs. 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults* Shows clinical effectiveness of 8 days of antibiotics as compared to 15 days, with the possible exception of non-fermenting gram-negative bacillus such as *Pseudomonas* species	2003 Chastre J, et al. JAMA 2003;290:2588–98

Images

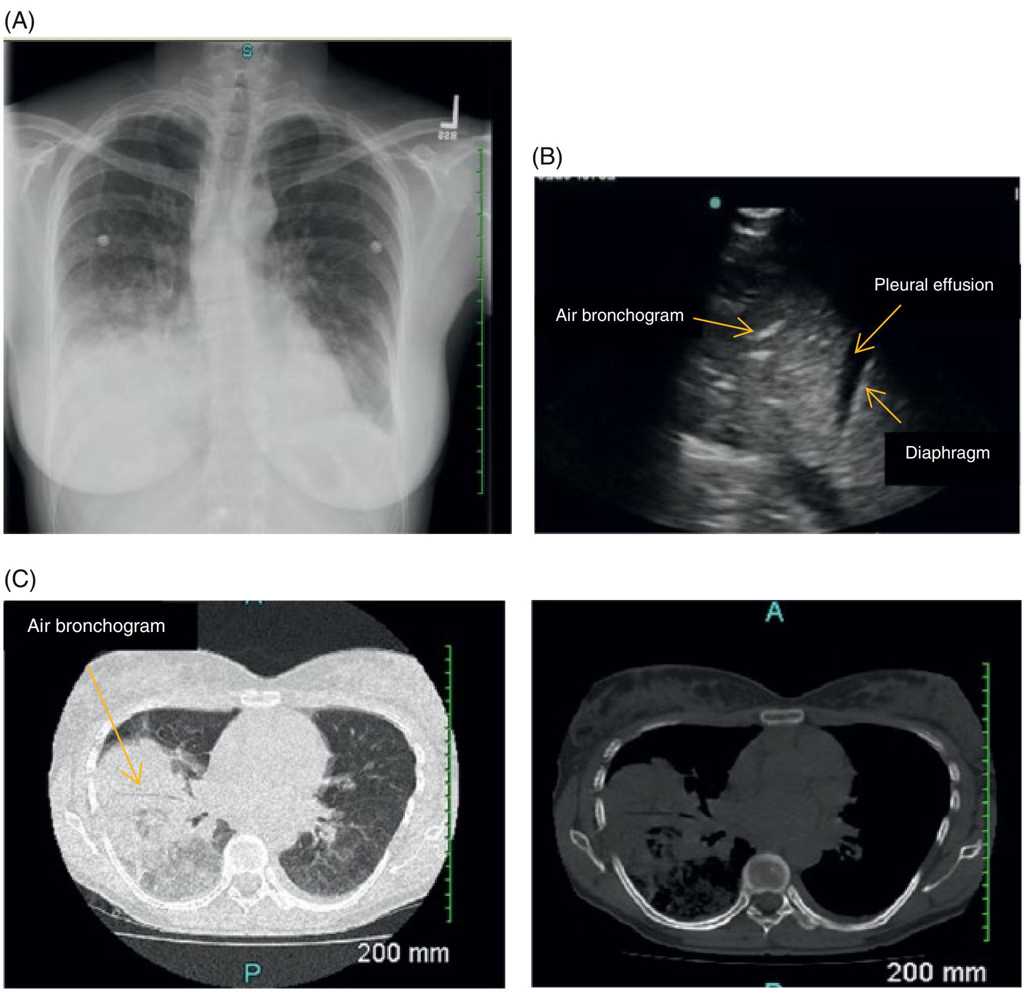

Figure 46.1 (A) Chest radiograph of right middle lobe (RML) and right lower lobe (RLL) lobar consolidation in a patient with CAP. (B) Ultrasound of same patient where the lung appears airless like a solid organ. (C) CT chest of same patient demonstrating extensive RML and RLL consolidation with air bronchograms.

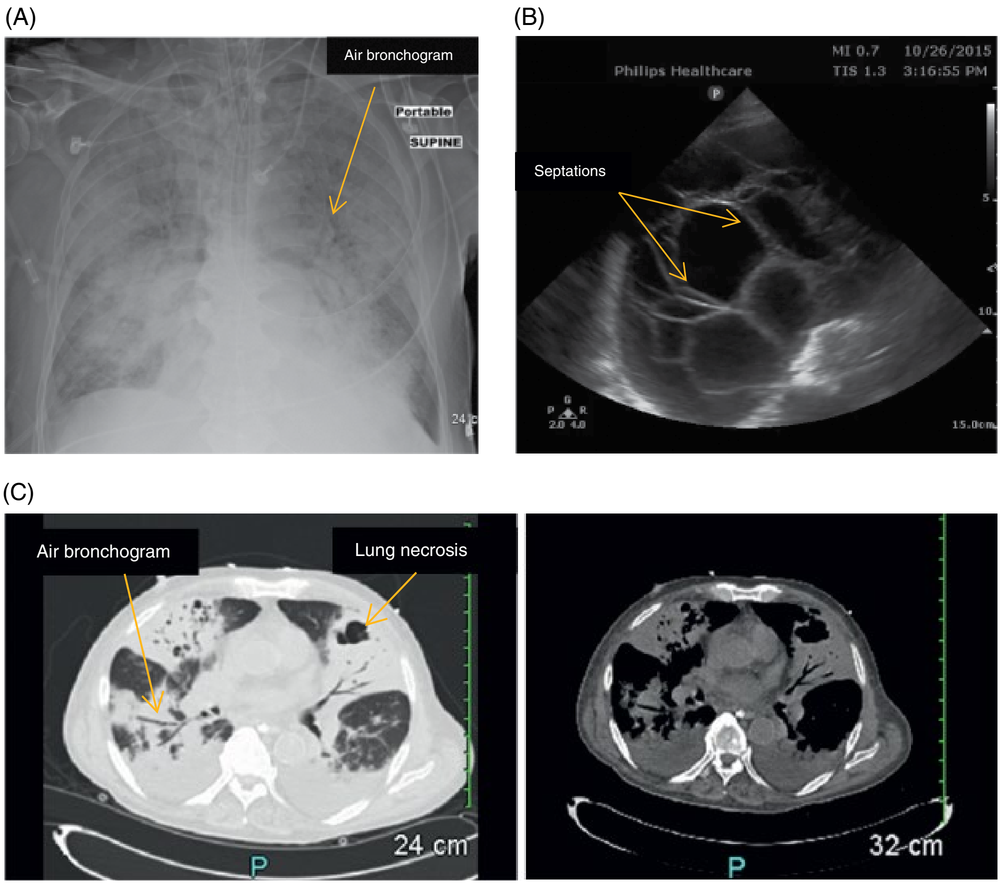

Figure 46.2 (A) Chest radiograph of an ICU patient with severe influenza pneumonia and superimposed MRSA pneumonia. Note the multilobar opacities with air bronchograms indicating consolidation. (B) Ultrasound of same patient whose small pleural effusion developed into a larger, loculated, and septated parapneumonic effusion. (C) CT chest of same patient demonstrating multilobar consolidation, necrotizing pneumonia, and small pleural effusions.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 47

Central Nervous System Infections

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OVERALL BOTTOM LINE

- Central nervous system infections are medical emergencies which must be diagnosed and treated with urgency.
- Most frequently encountered CNS infections are meningitis, encephalitis, and abscesses of the brain and spinal cord.
- Even with appropriate treatment, patients may still suffer significant morbidity and mortality.
- When treating meningitis, consider adding acyclovir for HSV encephalitis until the HSV PCR is negative.
- Surgical evaluation is required for CNS abscesses.

Background

Definition of disease

- Meningitis is an inflammation of the leptomeninges usually caused by an infection of the CSF surrounding the brain and spinal column. The presence or absence of alterations of consciousness and/or cognitive dysfunction distinguishes meningitis from encephalitis.
- A brain or spinal cord abscess is a focal collection within the CNS parenchyma.

Disease classification

- Meningitis and encephalitis are classified by duration of symptoms as acute, subacute (several weeks), or chronic (lasting at least 1 month).

Incidence/prevalence

- Meningitis is one of the top 10 infectious causes of death worldwide.
- Between 2003 and 2007 there were 4100 cases of bacterial meningitis with 500 deaths in the USA.
- Worldwide data report an annual incidence of acute encephalitis ranging from 3.5 to 7.4/100 000 in adults.
- The incidence of brain abscess in developed countries is as low as 1–2%, while in developing countries it is as high as 8%.

Etiology

Meningitis

- Meningitis can be differentiated into community-acquired and health care-associated (includes penetrating trauma). The pathogen varies by age group. Health care-associated meningitis is seen in post-surgical patients and pathogens include *Staphylococcus aureus*, coagulase-negative staphylococci, and aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*).

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Common causes of community-acquired bacterial meningitis

By age group	<1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella* species
	1–23 months	*Streptococcus pneumoniae, Neisseria meningitidis*, *Haemophilus influenzae* type b, *S. agalactiae, E. coli*
	2–50 years	*N. meningitidis, S. pneumoniae*
	>50 years	*S. pneumoniae, N. meningitidis, L. monocytogenes*

Other causes of meningitis

Bacterial	Spirochetes	*Treponema pallidum, Borrelia burgdorferi*
	Tick-borne	*Rickettsia rickettsii,* Erlichiosis
		Tuberculosis
Viral	Non-arthropod-borne viruses	Picornavirus (RNA), enteroviruses (echovirus, Coxsackie A, Coxsackie B, enterovirus, poliovirus), herpes simplex virus type 2 (HSV-2), mumps, HIV
	Arthropod-borne viruses	Togavirus (alphavirus, RNA), Eastern equine encephalitis (EEE), Western equine encephalitis (WEE), Venezuelan equine encephalitis (VEE), flavivirus (RNA), St. Louis encephalitis (SLE), West Nile virus (WNV), California encephalitis
Fungal meningo-encephalitis		*Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans, Cladosporium* spp., *Histoplasma capsulatum, Paracoccidioides brasiliensis*

Encephalitis

- Encephalitis is typically caused by viruses but also atypical bacteria, fungi, and parasites.
- The most common cause of viral encephalitis is herpes simplex: HSV-1 is most common in adults and HSV-2 is most common in infants (Figure 47.1).

Causes of encephalitis

Viral	Herpes simplex, varicella-zoster, Epstein–Barr, cytomegalovirus, enteroviruses, measles, mumps, rubella Vector-borne: West Nile, St. Louis encephalitis, Eastern equine encephalitis, Western equine encephalitis, Japanese encephalitis, rabies
Bacterial	*Mycoplasma, Mycobacterium, Treponema pallidum* (syphilis) Vector-borne: *Bartonella, Rickettsia* (Rocky Mountain spotted fever), *Ehrlichia, Borrelia, Coxiella* (Q fever)
Fungal	*Coccidioides, Cryptoccoccus, Histoplasma*
Parasitic	*Toxoplasma, Plasmodium falciparum, Acanthamoeba, Taenia*

Brain abscess

- Common causes of brain abscess (appear as ring-enhancing lesions):
  - *Staphylococcus aureus*.
  - *Streptococcus*.
  - Anaerobes.
  - Toxoplasmosis – most common CNS space-occupying lesion in AIDS.
  - *Taenia solium* – larval cysts causing cysticercosis.
  - Mucormycosis leading to rhino-orbital-cerebral infection.

Epidural abscess

- Common causes of epidural abscess:
  - *Staphylococcus aureus, Streptococcus*, gram-negative bacilli.

Pathology/pathogenesis

Meningitis

- A pathogen enters through the bloodstream, crosses the blood–brain barrier (BBB), and replicates in the CSF space.
- Many of the meningeal bacterial cell wall products (such as lipopolysaccharide and peptidoglycan) can induce an inflammatory host response.
- Several CNS-specific cells such as cerebromicrovascular endothelial cells, astrocytes, and microglia are capable of producing TNF-α, IL-1β, and IL-6, which are early pro-inflammatory cytokines. These in turn stimulate a downstream production of other cytokines, arachidonic acid metabolites, chemokines, and reactive nitrogen and oxygen intermediates.
- In response, leukocytes migrate to the subarachnoid space and once activated release cytotoxic agents that cause direct cellular injury.
- Bacterial DNA released during autolysis may have an additional inflammatory effect. Bacterial DNA can stimulate macrophages and pro-inflammatory mediators such as TNF-α.
- The inflammatory response leads to edema, cerebral hypoperfusion, and elevated intracranial pressure in a vicious cycle of continued neuronal injury.

Encephalitis

- Some viruses are transferred to humans from an infected animal bite or through exposure to their secretions. Some viruses may enter the CSF space by crossing the BBB, others travel along neuronal pathways.
- Viruses enter neural cells causing cellular malfunction, perivascular congestion, hemorrhage, tissue necrosis, and trigger an inflammatory response that disproportionately affects gray matter.
- When associated with evidence of meningeal irritation and CSF pleocytosis, it is referred to as meningoencephalitis.
- Enteroviruses are the most common cause of viral meningoencephalitis (VME). During summer months, arboviruses commonly cause VME. Several herpetic family viruses can cause VME.

Brain abscess

- This begins with cerebritis, an area of unencapsulated infection of the brain parenchyma that develops into a collection of pus. Abscesses are typically seen following trauma, surgery, hematogenous dissemination of organisms during systemic infection, or direct extension. Inflammation recruits neutrophils, which leads to vasogenic edema. After 2 weeks a vascularized capsule forms and the collection becomes walled off (Figure 47.2).
- Abscesses may arise from direct extension from nearby structures such as teeth, bone, sinus mucosa, internal auditory canal, or cochlear structures. Otogenic infections are the most common source.
- Less commonly, abscesses may develop from hematogenous spread from an infection in the lung, endocardium, pelvis, abdomen, or skin and soft tissues.

Spinal epidural abscess

- Infection of the potential space between the dura mater of the spinal cord and the vertebral body, caused by hematogenous spread, direct extension from an adjacent structure, or from a procedure, trauma, or other manipulation of the spinal cord. In a minority of cases the mechanism is unknown.
- A spinal abscess (Figure 47.3) may cause a neurologic deficit either from direct compression of the spinal cord or by vascular occlusion by microthrombi.

Predictive/risk factors for CNS infection

Risk factor	Pathogen
Lack of childhood or adult vaccinations	VZV, measles, mumps, rubella
Age	*Streptococcus pneumoniae*, *Listeria monocytogenes*, TB, gram-negative organisms
Communal living – college dorms, military bases, boarding schools, child care facilities	*Neisseria meningiditis*
Pregnancy	*L. monocytogenes*
Immunocompromised state – AIDS, alcohol abuse, diabetes, asplenia, use of immunosuppressive or chemotherapeutic drugs	*S. pneumoniae, L. monocytogenes, N. meningiditis*, CMV, fungal
Mosquito exposure	West Nile, Dengue, Japanese, Eastern equine, Western equine, St. Louis, yellow fever
Tick exposure	*Rickettsia, Borrelia, Ehrlichia*
Animal exposure	Lymphocytic choriomeningitis virus (rodent), cat-scratch disease (cat), brucellosis or Q fever (cattle), leptospirosis (infected animal urine)
Cranial or spinal surgical procedures	Staphylococcal species, gram-negative organisms

Prevention

Screening

- There is no recommended screening test for meningitis or encephalitis. Patients who have a personal or family history of two or more episodes of meningococcal or pneumococcal meningitis should have immunologic testing.
- All patients with meningitis should be screened for HIV.
- Patients with a recent history of neurosurgery, trauma, and evidence of rhinorrhea or otorrhea should have an investigation for CSF leak. Cranial bone defects are evaluated with high resolution CT scan. Diagnosing a CSF leak may require cisternography.
- Patients who develop recurrent brain abscesses require evaluation for vascular malformations.

Primary prevention

- There are vaccines available for three types of bacterial meningitis: *Neisseria meningitides*, *Streptococcus pneumoniae*, and *Haemophilus influenza* type b (Hib) and for polio, measles, mumps, and rubella. Please refer to the CDC website for vaccine schedules: http://www.cdc.gov/vaccines/schedules/.
- Persons who come into close contact with patients with meningococcal meningitis should be offered antibiotic prophylaxis.
- Antibiotics may also be recommended for household contacts of a patient with a severe Hib infection.
- Certain CNS infections require strict isolation:
  - Contact precautions: MRSA infections and disseminated HSV.
  - Droplet precautions: *N. meningitidis*, Hib, rubella, and mumps.
  - Airborne precautions: TB, varicella, and measles.

Secondary prevention

- Indwelling devices such as ventricular drains or shunts, Ommaya reservoirs, or cochlear implants should be removed.
- Bony defects or CSF leaks that cause recurrent infections may ultimately require surgical repair.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Patients with meningitis typically present with fever, neck stiffness, and altered mental status, though they may not have all three findings at presentation.
- A careful and thorough neurologic exam is required, paying close attention to focal neurologic deficits and nuchal rigidity.
- Focal findings are not typical in meningitis and should increase the suspicion for encephalitis or abscess.
- While brain imaging is required for suspected brain abscess, unnecessary imaging in meningitis and encephalitis may delay lumbar puncture and initiation of antibiotics.
- All patients with suspected meningitis or encephalitis require a lumbar puncture (LP) for CSF analysis. However, if the LP must be delayed, antimicrobial treatment should be given prior to LP.
- Clinicians should consider arboviruses in the differential diagnosis cases with aseptic meningitis and encephalitis during the summer months.

Differential diagnosis

Meningitis, encephalitis, and brain abscesses can all mimic each other and so all should be considered for the patient.

Differential diagnosis	Features
Paraneoplastic encephalitis	Patients may present with classic syndromes associated with cancer with or without a cancer diagnosis: limbic encephalitis, subacute cerebellar degeneration, subacute sensory neuropathies, opsoclonus myoclonus ataxia, dermatomyositis, Eaton–Lambert syndrome
Autoimmune encephalitis	May present with a prodromal viral-like illness. Neurologic findings are specific to the causal antibody. Should be suspected with associated non-specific CSF findings. Anti-NMDA receptor encephalitis can present with psychiatric manifestations, memory deficits, seizures, and stupor with catatonic features
Metabolic encephalopathy	Global cerebral dysfunction in the setting of a systemic illness. Common in the critically ill
Primary angiitis of the CNS	Should be suspected when a young person presents with recurrent TIAs or strokes. Requires neuroimaging and angiography
Drug-induced meningitis	History of medication use: non-steroidal anti-inflammatory, sulfa antibiotics, intravenous immunoglobulins, antiepileptics, OKT3 antibodies
Leptomeningeal carcinomatosis	Typically has multifocal involvement
Subarachnoid hemorrhage	Classic presentation is of sudden severe headache – 'worst headache of my life'
Subdural hematoma	Subacute or chronic hematomas will usually have a remote history of fall or trauma, may have an exacerbating acute component
Neurosarcoidosis	Patients typically have lung involvement, though not always
Toxidromes	Acute ingestion or drug use/abuse history
Post-infectious acute disseminated encephalitis and encephalomyelitis	History of illness or vaccination days to months prior to onset of symptoms. Motor deficits predominate, but sensory deficits may also be present
Spondylitis, spondylarthritis, discitis	Neck or back pain that may worsen over weeks to months, usually worse with activity and relieved by rest

Typical presentation

- Presentations of CNS infections can be as varied as the potential underlying etiologies. Common features of meningitis and encephalitis are fever and altered mental status. However, brain and spinal epidural abscesses often present without fever.
- Signs of meningeal irritation, such as nuchal rigidity and photophobia, distinguish meningitis from other CNS infections.
- Focal findings raise suspicion for encephalitis or abscess.
- Point tenderness is an important feature of spinal epidural abscess.

Clinical diagnosis

History

- The timeframe from onset of symptoms may differentiate the etiology. Acute onset <48 hours is often bacterial. A subacute onset is more typical of viral illnesses, while chronic or smoldering symptoms are more typical of fungal, parasitic, or non-infectious causes.
- Classic features of both bacterial and viral meningitis include fever, headache, stiff neck, and altered mental status. Other symptoms include photophobia, nausea, vomiting, poor appetite, and lethargy.
- Brain abscesses will often present with headache, but lack the other features of fever and altered mental status. The physician should ask about subtle neurologic signs over past days or weeks.
- Features of epidural abscess include back pain, point tenderness, with or without focal neurologic deficit.
- It is very important to obtain history of HIV infection, other immunocompromised states, TB history or exposure, vaccination status, country of origin and travel, recreational activities, exposure to animals or insects, and occupational exposure. Medical and surgical history should include history of prior meningitis, brain or spine surgery, spine injections, and trauma.

Physical examination

- Vital sign assessment for temperature and hemodynamic stability.
- Complete neurologic exam should be performed: mental status, cranial nerves, motor and sensory examination, reflexes, and coordination. Focal findings indicate encephalitis or epidural or parenchymal abscess.
- Altered mental status often indicates bilateral hemispheric or brainstem dysfunction and significantly limits the ability to determine if the patient's neurologic evaluation is non-focal.
- An evaluation of nuchal rigidity, meningismus with decreased range of motion, Brudzinski's sign (flexion at the neck elicits flexion at the hip or knees), and Kernig's sign (with hips and knees flexed against abdomen extension on knees should elicit resistance). These signs have poor sensitivity and their absence does not exclude CNS infection.
- Examination of the oral cavity, palate, and sinuses.
- A thorough examination of the skin for rashes, purpura, erythema migrans, or vesicles.
- Examination of spine for point tenderness in epidural abscess.

Disease severity classification

- Bacterial meningitis carries a high risk of morbidity and mortality. Three clinical risk factors have been associated with adverse outcome: altered mental status, hypotension, and seizures.
- Patients with no clinical risk factors are considered low risk for morbidity and mortality. Patients with one risk factor are at intermediate risk. Patients presenting with two or more risk factors carry a high risk.
- A delay in initiation of appropriate antibiotics increases the risk of poor outcome.
- A delay in draining an epidural abscess increases the risk of poor neurologic outcome.

Laboratory diagnosis

List of diagnostic tests

- Initial blood tests: complete blood count, chemistries, coagulation parameters.
- Two sets of blood cultures. Blood cultures may be positive in *S. pneumoniae* and *N. meningitidis*.
- Lumbar puncture:
  - The incidence of brain herniation following LP is low. Patients with focal findings or an immunocompromised state (including HIV infection) should undergo non-contrast head CT to exclude a space-occupying lesion prior to LP.
  - Opening pressure.
- CSF studies: always obtain cell count with differential, glucose, protein, gram stain, and bacterial culture (Table 47.1).
  - CSF for HSV PCR.
  - West Nile virus encephalitis should be suspected and tested for in patients with fever, altered mental status, and acute flaccid paralysis during mosquito season (cases peak in the summer months).
  - According to CDC recommendations, in cases with suspected arbovirus encephalitis, serum and CSF samples should be obtained for serologic testing and cases should be reported promptly to state health departments.
  - Cryptococcal antigen.
- HIV testing.
- EEG: for patients with a persistent depressed level of consciousness despite appropriate therapy.

List of imaging techniques

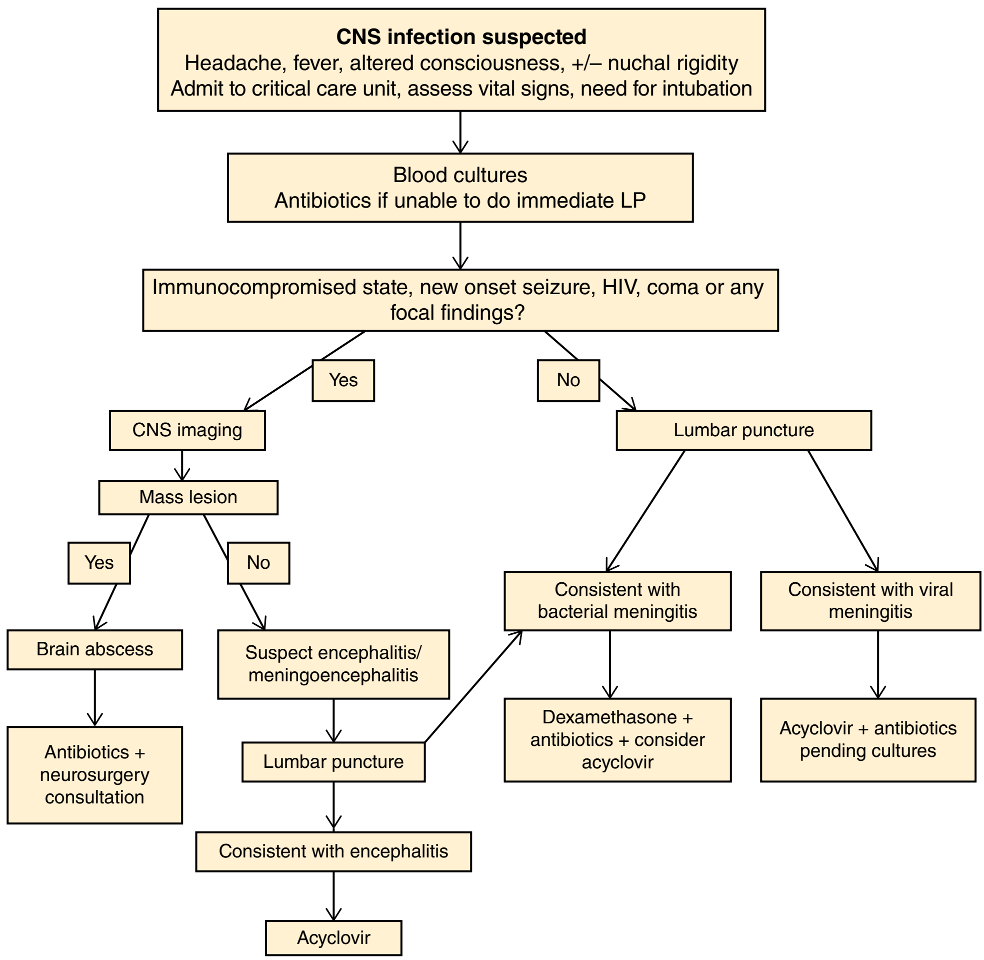
- CT scan to exclude a space-occupying lesion or cerebral edema with associated mass effect: a non-contrast study should be obtained prior to LP for any patient with an immunocompromised state (e.g. HIV infection, immunosuppressive therapy), history of CNS disease, new onset seizure, papilledema, abnormal level of consciousness, or focal neurologic deficit.
- Contrast-enhanced CT: a rapid way to determine size and location of brain abscesses. CT of the spine may reveal narrowing of the disc space or bone erosion indicating a discitis or osteomyelitis.
- MRI with IV gadolinium: the diagnostic test of choice for both brain and spinal epidural abscesses.

Table 47.1 CSF findings in various forms of CNS infection.

	Normal	Bacterial	Viral	Fungal	TB
Opening pressure (cmH_2O)	5–20	↑↑↑	↑	↑↑	↑↑
Appearance	Clear	Turbid	Clear	Clear	Fibrin web
Protein (mg/dL)	12–60	↑↑↑	Normal to ↑	↑↑	↑↑
Glucose (mg/dL)	40–70	↓↓↓	Normal	↓	↓
Cell count (/μL)	0–5	>1000	100–1000	100–500	10–1000
Cell differential		Polymorphonuclear neutrophils	Lymphocytic	Mixed or lymphocytic	Mixed, lymphocytic, or monocytic

Diagnostic algorithm (Algorithm 47.1)

Algorithm 47.1 **Evaluation and management of suspected CNS infection**



Potential pitfalls/common errors made regarding diagnosis of disease

- Delay in diagnosis due to lack of history.
- Presuming drug or alcohol as the cause of altered consciousness.

Treatment

Treatment rationale

- *Bacterial meningitis* is a medical emergency. Prompt initiation of antibiotics within 60 minutes of arrival is crucial even before CSF gram stain and culture results are known (see Algorithm 47.1). Corticosteroids (dexamethasone 0.15 mg/kg every 6 hours for 4 days) are recommended before or at the time of antibiotic administration for suspected bacterial meningitis. Empiric antibiotics must cover all potential pathogens, based on age and immune status.

- *Viral meningitis* requires supportive treatment and acyclovir for possible HSV.
- *Viral encephalitis* typically requires hospitalization for supportive management. Prompt administration of acyclovir for possible HSV should be initiated in all suspected encephalitis. Any delay in acyclovir therapy worsens prognosis. Development of seizures is common and is an independent factor for increased morbidity and mortality. Management includes monitoring for signs of intracranial hypertension, maintaining normothermia, and avoiding hyponatremia. Conditions that mimic infectious encephalitis should be considered, particularly if no etiology is identified in the first week of hospitalization.
- *Brain and spinal epidural abscesses* require antibiotics and may require drainage
- *Iatrogenic infections* of the CNS are usually complications of neurosurgical procedures, LP, and spinal injections. Intracranial shunt infections require a complete antibiotic course and removal of infected shunt.

Managing the hospitalized patient

Meningitis

- Empiric antibiotics should be administered within 60 minutes to all patients with bacterial meningitis (Table 47.2). Antibiotics should be modified based on gram stain and culture; after 48–72 hours, most routine CSF cultures will show preliminary results.
- Antibiotic duration: although guidelines recommend the following duration of therapy, therapy must be individualized based on the clinical response to treatment:
  - *N. meningitidis*, *H. influenzae*: 7 days.
  - *Streptococcus agalactiae*, *S. pneumoniae*: 10–14 days.
  - Aerobic gram-negative bacilli, *Listeria monocytogenes*: 21 days.

Table 47.2 Antibiotic regimens for meningitis.

Predispositions	Likely pathogens	Preferred antimicrobials
<1 month	Group B streptococci, *Escherichia coli*, *Listeria monocytogenes*	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1–23 months	*Streptococcus pneumoniae*, *Neisseria meningitidis*, group B streptococci, *Haemophilus influenzae*, *E. coli*	Vancomycin plus third-generation cephalosporin[a,b]
2–50 years	*N. meningitidis, S. pneumoniae*	Vancomycin plus third-generation cephalosporin[a,b]
>50 years	*S. pneumoniae, N. meningitidis*, *L. monocytogenes*	Vancomycin plus third-generation cephalosporin[a,b] plus ampicillin
Impaired immunity	*L. monocytogenes*, gram-negative bacilli, *S. pneumoniae*	Ampicillin plus ceftazidime or meropenem plus vancomycin
Cerebrospinal fluid leak or basilar skull fracture	*S. pneumoniae*, various streptococci, *H. influenzae*	Vancomycin plus third-generation cephalosporin[a]
After neurosurgery or penetrating trauma	*Staphylococcus aureus*, coagulase-negative staphylococci, gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime or vancomycin plus ceftazidime or vancomycin plus meropenem
Cerebrospinal fluid shunts (external or internal)	Coagulase-negative staphylococci, *S. aureus*, aerobic gram-negative bacilli (including P. aeruginosa), *Propionibacterium acnes*	Vancomycin plus cefepime
Tick season	*Borrelia* species, rickettsial species, *Ehrlichia*	Doxycycline added

[a] Ceftriaxone or cefotaxime.
[b] If dexamethasone is administered consider adding rifampin.

- Repeat lumbar puncture: in patients with uncertain etiology and lack of clinical improvement.
- Adjunctive dexamethasone: guidelines suggest dexamethasone administration before or at time of antibiotic administration to reduce unfavorable neurologic outcomes and death.
  - This benefit was seen in a subgroup of patients with pneumococcal meningitis, and not for meningitis caused by other pathogens.
  - Dexamethasone 0.15 mg/kg is given 20 minutes before or at the time of administration of antimicrobial agents, then continued every 6 hours for 4 days if *S. pneumoniae* is diagnosed. If cultures do not show *S. pneumoniae*, dexamethasone should be discontinued.
  - If antibiotics have already been given, guidelines recommend not giving dexamethasone.
  - If vancomycin is used for treatment of meningitis resulting from highly cephalosporin-resistant *S. pneumoniae*, rifampin may be added, as dexamethasone may reduce the CSF concentration of vancomycin.

Encephalitis

- Acyclovir must be administered parenterally (10 mg/kg IV every 8 hours with dose adjusted in patients with impaired creatinine clearance) to achieve therapeutic levels in brain parenchyma.
- Empiric antiviral treatment should be started immediately and continued until HSV-1 has been reasonably excluded, which may require testing serial CSF samples.
  - HSV PCR may be negative on initial LP and should be repeated if suspicion persists.
  - Intravenous acyclovir is continued for 14–21 days.
  - Ganciclovir and foscarnet are administered for CMV encephalitis.

Brain abscess

- Empiric antibiotic therapy should be started prior to surgical drainage (Table 47.3). HSV PCR may be negative on initial LP and should be repeated if suspicion persists.
- Duration of treatment is usually 4–6 weeks if the abscess is drained or 6–8 weeks if not drained. Management should be guided by biweekly imaging up to 3 months until clinical recovery.
- Abscesses of 2.5 cm should be surgically excised or drained stereotactically.
- For abscesses <1.5 cm with a high risk of surgical complications and no neurologic deficits, medical therapy alone is often successful.

Table 47.3 Antimicrobials for brain abscess.

Predisposing condition	Antimicrobial treatment
Dental abscess	Penicillin plus metronidazole
Chronic otitis	Ceftriaxone plus metronidazole
Sinusitis	Ceftriaxone plus metronidazole
Penetrating trauma	Vancomycin plus third-generation cephalosporin[a] plus metronidazole
Bacterial endocarditis	Vancomycin plus ceftriaxone plus metronidazole
Pulmonary infection	Penicillin plus metronidazole plus TMP-SMX
HIV infection (toxoplasmosis)	Pyrimethamine plus sulfadiazine plus folinic acid
Postoperative neurosurgical	Vancomycin plus ceftazidime or cefepime or meropenem
Diabetes mellitus (*Mucor*)	Amphotericin B

[a] Ceftriaxone or cefotaxime.

- In HIV infected patient: pyrimethamine plus sulfadiazine plus folinic acid for empiric treatment of toxoplasmosis.
- IV dexamethasone can be used for vasogenic edema.
- Undrained abscess should have follow-up imaging within days.
- Mucormycosis in immunosuppressed and diabetic patients requires aggressive surgical debridement and early antifungal therapy.

Spinal epidural abscess

- Patients presenting with spine pain, but no deficits and no risk factors for medical failure (advanced age, diabetes, MRSA infection, bacteremia), may be treated conservatively with antibiotics, but require close follow-up for delayed neurologic deterioration.
- If blood cultures are negative, CT-guided aspirate should be done.
- Patients with a neurologic deficit require surgical drainage.
- Empiric antibiotics should include vancomycin and cefotaxime or ceftriaxone. If *Pseudomonas* is possible, cefepime or ceftazidime should be added to vancomycin.

Prevention/management of complications

Non-neurologic complications

- Hypotension and shock must be treated to maintain cerebral perfusion pressure.
- Hyponatremia can contribute to brain swelling.
- Coagulation disorders frequently occur with bacteremia. Patients with meningococcemia may develop fulminant disseminated intravascular coagulation.
- Septic complications include endocarditis, pyogenic arthritis, and prolonged fever.

Elevated intracranial pressure

- Management goals are to break the cycle of raised ICP and cerebral ischemia at the earliest, maintain an adequate cerebral perfusion pressure, and prevent brain herniation.
- Patients with suspected intracranial hypertension should have an ICP monitor placed.
- Treatment strategies include head-of-bed elevation, osmotic therapy with mannitol or hypertonic saline, sedation and analgesia with intubation and mechanical ventilation, therapeutic neuromuscular blockade, or CSF diversion.
- Dexamethasone should be used in patients with vasogenic edema regardless of the suspected organism.
- Patients without focal findings, but with persistent or late onset obtundation or coma may have developed brain swelling, subdural effusion, hydrocephalus, ventriculitis, cortical thrombophlebitis, or venous sinus thrombosis.
- Patients with encephalitis and cerebral edema are best managed in an intensive care setting with close neurologic monitoring.
- All patients with depressed consciousness require electroencephalography to diagnose or manage non-convulsive status epilepticus.

Clinical pearls

Septic intracranial thrombophlebitis

- Septic cavernous sinus thrombosis is the most common site of septic thrombosis. *Staphylococcus* is the most commonly identified organism. Symptoms include fever, periorbital pain, and swelling.
- The infection reaches the cavernous sinus through venous spreading. Requires early imaging, and specific antibiotic therapy. Surgery is used to treat the nidus of infection, if required. The role of anticoagulation is not well established.

Bacterial infections

Bacteria	Important clinical points
Streptococcus pneumoniae	Most common cause of meningitis in patients >18 years of age
Neisseria meningitidis	Young people in communal living particularly at risk. Prophylaxis for people in close contact: ciprofloxacin, rifampin, or ceftriaxone
Listeria monocytogenes	Neonates, older adults, pregnant women, and immunosuppressed patients are at increased risk
Mycobacterium TB	Complication of primary TB Involves base of the brain Vasculitis and scarring
Treponema pallidum	Meningovascular syphilis: infectious small vessel endarteritis causing ischemic strokes. Middle cerebral artery is the most commonly affected with associated basal ganglia infarcts Tabes dorsalis: involves posterior root ganglia and posterior column; causes ataxia, absent deep tendon reflexes, Argyll Robertson pupil
Leptospira interrogans (leptospirosis)	Presents as two distinct clinical syndromes: • Anicteric leptospirosis has two well defined stages: septicemic stage (after 7–12 days incubation period) with conjunctival suffusion as the most characteristic physical finding, and immune stage that is characterized by aseptic meningitis • Icteric leptospirosis: potentially fatal syndrome with jaundice, renal failure, hypotension, and hemorrhage
Anthrax (meningitis)	Life-threatening illness with meningeal component Initial non-specific flu-like symptoms followed by a second phase of hemodynamic collapse and multiple organ failure Add either penicillin or chloramphenicol

Viral infections

Virus	Important clinical points
Enteroviruses (meningitis and encephalitis)	Most common cause of viral meningitis. Coxsackie and echoviruses make up the majority of cases
Arboviruses (encephalitis)	Encephalitis can be fatal. They have both geographic and seasonal distributions. Usual vectors are mosquitoes and ticks
CMV (encephalitis)	Most common viral CNS infection in AIDS
Herpes simplex virus type 1 (meningitis and encephalitis)	Causes hemorrhagic necrosis of the temporal lobes
Human rabies (encephalitis)	The CDC recommends that human rabies should be considered in the differential diagnosis of patients presenting with unexplained rapidly progressive encephalitis Classic presentation is encephalitis with hypertonicity and hypersalivation
HIV (encephalitis)	Symptoms can be mistaken for progressive multifocal leukoencephalopathy caused by the JC virus

Fungal and parasitic infections

Fungus/parasite	Important clinical points
Cryptococus neoformans (meningitis and encephalitis)	Occurs in an immunocompromised host; most common fungal CNS infection in AIDS; budding yeast seen with India ink stain
Mucor species (frontal lobe abscess)	Occurs in diabetic ketoacidosis; spreads from frontal sinuses
Naegleria fowleri (meningoencephalitis)	Protozoa (amoeba) involves frontal lobes; contracted in freshwater lakes
Trypanosoma brucei gambiense *Trypanosoma brucei rhodesiense* (encephalitis)	Protozoa (hemoflagellate); transmitted by an infected tsetse fly Diffuse encephalitis: somnolence Treatment: pentamidine early; melarsoprol in encephalitis stage
Taenia solium (cysticercosis)	Helminth (tapeworm; cestode); transmitted by pigs Calcified cysts cause seizures and hydrocephalus Treatment: albendazole + dexamethasone
Toxoplasma gondii (encephalitis)	Protozoa (sporozoan); most common CNS space-occupying lesion in AIDS; ring-enhancing lesions on CT Treatment: pyrimethamine + sulfadiazine + folinic acid

Special populations

Pregnancy

- Pregnant women are at increased risk of developing listeriosis. Infections can lead to miscarriage, stillbirth, premature delivery, and meningitis in the newborn.
- Pregnant women should be screened for group B streptococci at 35–37 weeks of gestation. Women with positive culture should be treated with penicillin G (or clindamycin for a penicillin allergy) intra-partum to avoid transmission to the newborn.

Children

- <1 month: *S. agalactiae*, *E. coli*, *L. monocytogenes*, *Klebsiella*.
  - Treatment includes ampicillin plus cefotaxime or ampicillin plus an aminoglycoside.
- 1–23 months: *S. pneumonia, N. meningitidis, S. agalactiae, H. influenza, E. coli*.
  - Infections are an important preventable cause of neurologic disability in children. The key strategy for prevention is delivery of available vaccines.

Elderly

- *H. influenzae* (>50 years) and *L. monocytogenes* (>60 years) infections are more common in elderly populations. Ampicillin should be included in the empiric antimicrobial regimen.
- Prognosis of acute bacterial meningitis and acute viral meningitis is substantially worse in older adults.
- The high prevalence of cervical spine disease in older individuals may result in false positive tests for nuchal rigidity.

Others

- Patients with HIV infection: cryptococcal meningitis, toxoplasmosis brain abscess, and encephalitis must be considerations.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- The risk of death in patients with CNS infections depends on age (>50 years), level of consciousness (GCS score <6), onset of seizures within 24 hours of admission, signs of increased ICP, concurrent comorbidities including shock and severe neurologic impairment, and need for mechanical ventilation.
- Delay in initiation of treatment worsens prognosis.
- The mortality rate in bacterial meningitis also depends on the infecting organism. Pneumococcal meningitis carries the highest mortality (up to 20%), followed by *L. meningitis* (15%) and finally *H. influenzae*, *N. meningitidis*, or group B streptococci (3–7%).
- Sequelae of bacterial meningitis can occur in 25% of the survivors.
- Prognosis in adults with acute viral meningitis is excellent and the majority of patients attain full recovery.
- The prognosis of encephalitis is variable depending on the underlying cause, with mortality and neurologic sequelae being highest in Eastern equine encephalitis among all arthropod-borne encephalitis.
- With the advent of enhanced intracranial imaging techniques and appropriate neurosurgical procedures, the mortality rate of brain abscess has substantially decreased. Mortality rate is <15% and severe sequelae occur in >20% survivors. Cranial epidural abscess has a mortality <5%, with good neurologic function among survivors.

Natural history of untreated disease

- Untreated bacterial meningitis is almost always fatal.
- Viral meningitis gradually resolves and is rarely fatal.
- Untreated, the fatality in herpes encephalitis can approach 70%. Most survivors will have serious neurologic deficits.

Prognosis for treated patients

Outcomes vary depending on the causative agents. However, baseline features can be used to estimate an individual's risk for any adverse outcomes.

- Bacterial meningitis has a significant mortality rate despite antibiotic treatment. A recent population-based study between 2003 and 2007 showed a mortality rate of 16% in treated meningitis patients.
- Encephalitis: even with early administration of therapy, nearly two-thirds of survivors will have significant neurologic deficits. Even with appropriate diagnosis and treatment, mortality may still be as high as 20–30%.

Follow-up tests and monitoring

- Meningitis: if there is a lack of clinical response or uncertainty in the diagnosis, a repeat LP should be performed in 48 hours.
- Brain abscess: any sign of clinical deterioration requires emergent CNS imaging. Duration of antibiotics will be based on clinical and radiographic resolution.
- Spinal epidural abscess: serial clinical evaluations and follow-up MRI of the spine at approximately 4–6 weeks into therapy.

Reading list

AHRQ National Guideline Clearinghouse. Guideline summary: Vertebral osteomyelitis, discitis, and spinal epidural abscess in adults. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ), 2013. https://www.guideline.gov

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Tuchman A, Pham M, Hsieh PC. The indications and timing for operative management of spinal epidural abscess: literature review and treatment algorithm. Neurosurg Focus 2014;37(2):E8.
van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM. Community-acquired bacterial meningitis in adults. N Engl J Med 2006;354:44–53.

Suggested websites

http://www.cdc.gov/vaccines/schedules/
https://www.eaneurology.org/EAN-Guideline-Papers.1351.0.html
http://www.hopkinsmedicine.org/
http://www.idsociety.org/IDSA_Practice_Guidelines/

Guidelines

National society guidelines

Title	Source	Date and reference
Practice Guidelines for the Management of Bacterial Meningitis	Infectious Diseases Society of America (update in progress)	2004 Clin Infect Dis 2004;39(9):1267–84
The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America	Infectious Diseases Society of America	2008 Clin Infect Dis 2008;47:303–27

International society guidelines

Title	Source	Date and reference
EFNS Guideline on the Management of Community-Acquired Bacterial Meningitis: Report of an EFNS Task Force on Acute Bacterial Meningitis in Older Children and Adults	European Federation of Neurological Societies	2008 Eur J Neurol 2008;15:649
Viral Meningoencephalitis: A Review of Diagnostic Methods and Guidelines for Management	European Federation of Neurological Societies	2010 Eur J Neurol 2010;17:999–e57
Consensus Document on Controversial Issues for the Treatment of Infections of the Central Nervous System: Bacterial Brain Abscesses	International Society for Infectious Diseases	2010 Int J Infect Dis 2010;14(Suppl 4):S79

Evidence

Type of evidence	Title and comment	Date and reference
RCT	*Dexamethasone in Adults with Bacterial Meningitis* Adjunctive therapy of steroids has been shown to reduce morbidity and mortality among patients with acute bacterial meningitis, particularly *Streptococcus pneumoniae* meningitis	2002 N Engl J Med 2002;347(20):1549–56
Systematic review	*The Clinical Approach to Encephalitis*	2016 Curr Neurol Neurosci Rep 2016;16(5):45
Systematic review	*Brain Abscess* Outcome for patients with brain abscess has decreased a great deal with no neurologic sequelae over the past five decades	2014 N Engl J Med 2014;371:447–56

Images

Figure 47.1 HSV-1 encephalitis on MRI.

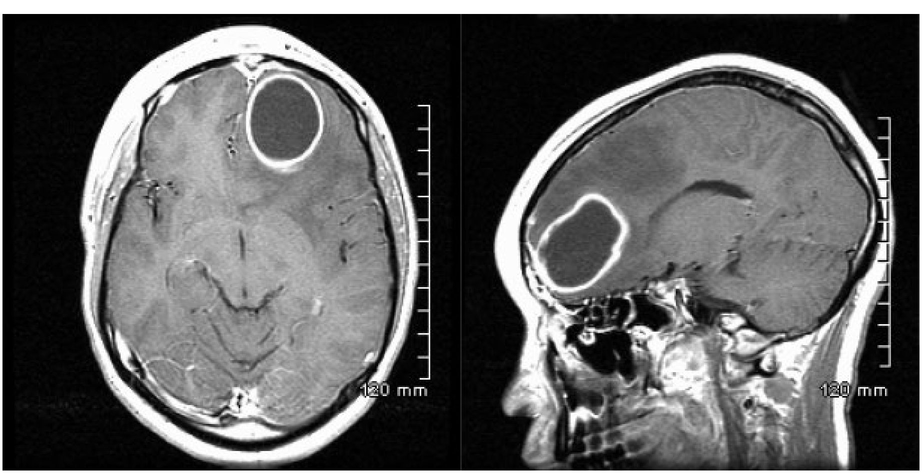

Figure 47.2 MRI with contrast showing ring enhancing abscess.

Figure 47.3 Spinal epidural abscess with vertebral osteomyelitis.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 48

Acquired Immune Deficiency Syndrome

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OVERALL BOTTOM LINE

- In the era of antiretroviral therapy (ART) for HIV, sepsis and non-HIV-related illness account for the majority of ICU admissions in this patient population.
- It is important to be aware of HIV-related critical illness from non-compliance with ART and in newly diagnosed HIV.
- Clinical suspicion and early initiation of treatment for bacterial infection and pneumocystis pneumonia (PCP) improves survival.
- Acute respiratory failure is the most common reason for ICU admission in patients with HIV infection and is often associated with non-opportunistic or opportunistic infections.
- The initiation or continuation of ART medication in critically ill HIV-infected patients should be considered on a case by case basis as several of these agents have serious drug interactions with medications that are frequently used in ICUs.

Background

Definition of disease

Acquired immune deficiency syndrome (AIDS) is a potentially life-threatening condition caused by human immunodeficiency virus (HIV) infection, in which depletion of CD4-bearing helper T cells (to ≤20% of normal) renders the patient highly vulnerable to life-threatening conditions.

Disease classification

- HIV infection is divided into HIV-1 and HIV-2.
- HIV-1 infection is widespread worldwide and HIV-2 infection is more common in western Africa.
- Third and fourth generation HIV antibody tests detect both HIV-1 and HIV-2 infection.
- CDC classification divides HIV infection into A, B, and C (Table 48.1).

Incidence/prevalence

- The syndrome of immunosuppression was first described in the USA in 1981 when homosexual men were reported to have unusual infections like *Pneumocystis jiroveci* pneumonia (PCP) and a rare malignancy, Kaposi's sarcoma. In 1986 it was officially named HIV.
- Worldwide 37 million people live with HIV and a majority of them are in sub-Saharan Africa.
- The CDC estimated 1.2 million people in the USA were infected with HIV by the end of 2012.
- About 50 000 people contract new HIV infection every year.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Table 48.1 CD4 cell count categories.

	Clinical categories		
	A Asymptomatic, acute HIV infection, or PGL	**B** Symptomatic conditions, not A or C	**C** AIDS indicator conditions
≥500 cells/μL	A1	B1	C1
200–499 cells/μL	A2	B2	C2
<200 cells/μL	A3	B3	C3

PGL, persistent generalized lymphademopathy

- It is not unusual to make a new diagnosis of HIV infection in an ICU patient.
- Hepatitis C coinfection is common in HIV patients admitted to the ICU (as high as 35–60%) and is associated with higher short-term and long-term mortality.

Etiology

- HIV patients may be admitted to the ICU for various reasons depending on the organ system involvement.
- PCP may be responsible for 50–60% of ICU admissions in newly diagnosed HIV infection.
- The spectrum of disease causing ICU admission has changed with ART. The most recent observational studies continue to demonstrate respiratory failure as the most common ICU diagnosis.
- Mechanical ventilation is required in 40–60% of patients.

Causes of ICU admission in HIV-positive patients

Respiratory failure	40%
PCP	10–20%
Sepsis (including pneumonia)	10–20%
Neurologic	14%
Cardiac	10%
GI bleed	7%
Hematologic	6%
Metabolic	2%

Pathology/pathogenesis

- HIV virus infects and replicates in lymphocytes leading to destruction and gradual decrease of CD4 cells making the patient susceptible to opportunistic infections.
- CD4 count <200 cells/μL: PCP.
- CD4 count <100 cells/μL: *Toxoplasma*, *Aspergillus*, and CMV.
- CD4 count < 50/uL: *Mycobacterium avium*.
- Malignancy and *Mycobacterium* tuberculosis can occur at any stage with any CD4 cell count.

Predictive/risk factors

Severity of illness on admission to the ICU rather than CD4 cell count is a more reliable predictor of mortality.

Risk factor	Odds ratio for in-hospital mortality
Acute renal failure	4.2
Hepatic cirrhosis	3.8
Severe sepsis	3.7
Mechanical ventilation	3.5
ICU admission for coma	2.7
PCP	2.5

Prevention

- ART is a combination of two or more classes of antiretroviral medications used to limit replication of the virus and progression to AIDS.
- The success of ART in reducing progression of the disease has led to a reduction in ICU admissions for AIDS-related opportunistic infections.

Screening

- The CDC recommends screening all patients in all health care settings for HIV infection.
- Consent is required for HIV testing. For patients who lack capacity to consent, most states permit consent by the person lawfully authorized to consent for the patient's health care. For HIV testing for a patient without capacity, the CDC website includes individual state laws concerning HIV testing.

Secondary prevention

- Initiate appropriate prophylaxis for opportunistic infection per guidelines.

Diagnosis

Differential diagnosis

Differential diagnosis on initial presentation is broad, based on organ system involvement. There are multiple potential causes of acute respiratory failure, alteration in mental status, sepsis, seizures, gastrointestinal hemorrhage, multiorgan failure, hematologic disorders, and electrolyte/metabolic disturbances.

Typical presentation

- Typically, patients present with acute respiratory failure; the onset of respiratory symptoms may be acute, e.g. within days due to bacterial pneumonia, or slowly progressive dyspnea over weeks, e.g. in PCP.
- Respiratory symptoms: cough, fever, sputum production, tachypnea, fatigue, preceding upper respiratory infection (URI) symptoms.
- Meningitis and meningoencephalitis: altered mental status, headache, confusion lethargy, personality changes, and seizures. Fevers, neck stiffness, and photophobia are less common.
- Chronic liver disease: encephalopathy, alteration in sleep–wake cycle, melena, coffee ground emesis.
- Hematologic/oncologic: easy bruising, epistaxis, skin rash, bleeding manifestations, weight loss, night sweats, evening fevers.

Clinical diagnosis

History

History should include: recurrent infections, unexplained weight loss, fevers, night sweats, poly-substance or intravenous drug abuse, unprotected sex, men having sex with men, previous opportunistic infections, viral load, CD4 count, adherence to ART, and reason for previous ICU admission.

Physical examination

- In addition to a thorough general physical exam that is required for every patient admitted to ICU, focus on organ-specific examination findings:
- Respiratory: cough with or without purulent sputum, tachypnea, rhonchi, rales, bronchial breath sounds, and rarely hemoptysis.
- Neurologic: focal neurologic deficit, seizures, neck stiffness, Kernig's and Brudzinski's sign, lethargy, coma.
- Liver disease: scleral icterus, melena, hematemesis, hematochezia, ascites, palmar erythema, spider angioma, caput medusa, gynecomastia, testicular atrophy, splenomegaly.
- Hematologic/oncologic:
  - Thrombocytopenic patient: petechiae, purpura, jaundice, ecchymosis, splenomegaly.
  - Kaposi's sarcoma: blue-purple lesions on face, nose, legs, and gingival and buccal mucosa.
  - Non-Hodgkin's lymphoma: rubbery and enlarged cervical, supraclavicular, axillary, and inguinal lymph nodes and splenomegaly.
- Metabolic: lipodystrophy, central obesity.

Laboratory diagnosis

List of diagnostic tests

- Complete blood count:
  - Leukocytosis from bacterial infection such as pneumonia or urinary tract infection. Lack of leukocytosis in the setting of acute infection is not uncommon in advanced or newly diagnosed HIV with low CD4 counts.
  - Thrombocytopenia from HIV or autoimmune thrombocytopenia.
  - Anemia from gastrointestinal hemorrhage.
- Metabolic panel: elevated creatinine from acute kidney injury in sepsis, or HIV-associated nephropathy. Hyperkalemia and hyponatremia in patients with suspected adrenal insufficiency.
- AST, ALT, and bilirubin: may be elevated due to viral hepatitis, ART, or chronic liver disease.
- Lactate: elevated in severe sepsis or septic shock, hypoperfusion from cardiogenic shock, hepatic failure, and antiretroviral medications.
- LDH: elevated in hemolytic anemia, malignancy such as Hodgkin's or non-Hodgkin's lymphoma, and PCP.
- Arterial blood gas analysis: hypoxemia with low PaO_2/FiO_2 ratio <300 consistent with acute respiratory distress syndrome (ARDS), metabolic acidosis, and hypercapnia (e.g. in COPD).
- Blood and urine cultures: as indicated for infectious evaluation.
- Sputum specimen: bacterial and acid-fast bacilli cultures; PCR for influenza, parainfluenza, coronavirus, rhinovirus, and adenovirus are helpful in establishing etiology of respiratory infection.
- Bronchoscopy with bronchoalveolar lavage (BAL) for PCP has a high sensitivity of 97% (Figure 48.1). BAL can also diagnose bacterial pneumonia or tuberculosis (acid-fast bacilli) when sputum samples are inadequate. Bronchoscopic biopsy may be required for diagnosis of CMV pneumonia and also may increase the diagnostic yield for fungal or mycobacterial infections.
- Urine *Legionella* and pneumococcal antigen testing have high sensitivity and specificity compared with sputum cultures and remains positive after initiation of antibiotics.

- Lumbar puncture with cerebrospinal fluid (CSF) analysis: cell count with differential, gram stain, and cultures for bacterial meningitis, India ink stain for *Cryptococcus*, cryptococcal antigen, rapid plasma reagin test for syphilis, and HSV PCR and CMV PCR for meningoencephalitis. Increased opening pressure in crypotococcal meningitis indicates increased intracranial pressure.
- Hematologic/oncologic testing: peripheral blood smear to confirm thrombocytopenia and look for schistocytes in DIC and thrombotic thrombocytopenic purpura; D-dimer, fibrin split products, fibrinogen, PT, PTT, and INR in suspected DIC from severe sepsis/septic shock. Coombs test and haptoglobin for hemolytic anemia. Peripheral blood flow cytometry and bone marrow biopsy to investigate leukemia and lymphoma.
- Hepatitis viral serologies: hepatitis A, B, or C virus infection.
- Toxicology screen: based on clinical presentation.

List of imaging techniques

- CXR posteroanterior and lateral views: may be normal in as many as 20–25% of patients with PCP. Dense or focal air space opacity in bacterial pneumonia, diffuse bilateral interstitial or alveolar opacities in PCP (Figure 48.2), and pneumothorax from pneumocystis or mechanical ventilation.
- CT scan of chest: allows evaluation for pneumonia, pneumothorax, or lung mass in suspected lung cancer. PCP results in characteristic 'ground glass' reticulonodular infiltrates (Figure 48.3). CT also provides evaluation of mediastinal and hilar lymph nodes in suspected malignancy and fungal and mycobacterial infections.
- CT scan head/MRI head: cerebral edema, meningeal enhancement in meningitis/encephalitis, intracranial hemorrhage, or stroke. Primary CNS lymphoma with surrounding edema and toxoplasmosis lesions are better demonstrated on MRI.
- EEG: Evaluation of non-convulsive status epilepticus in altered mental status or coma.
- Ultrasound of liver: can diagnose cirrhosis and portal hypertension.
- CT scan and whole body PET scan: diagnosis and staging of cancer.

Potential pitfalls/common errors made regarding diagnosis of disease

- Coinfections are common in immunocompromised patients who are critically ill and should be suspected when patients do not respond to initial treatment (e.g. bacterial and pneumocystis pneumonia coinfection).
- Two or more disease processes can occur simultaneously and a high degree of clinical suspicion is required for diagnosis (e.g. hepatic encephalopathy and cerebral ischemic infarcts from embolic infective endocarditis in a comatose patient).
- HIV-infected patients are at increased risk of accelerated atherosclerosis, poorly controlled diabetes mellitus, hyperlipidemia, acute kidney injury, renal failure, and coinfection with hepatitis B and hepatitis C. Therefore, patients may be admitted to the ICU with myocardial infarction, heart failure, DKA, renal failure and hepatic encephalopathy – in the absence of infection.

Treatment

Treatment rationale

- Acute respiratory failure is the most common admitting diagnosis to ICU and up to 50% of all patients undergo invasive mechanical ventilation; 70–80% of these patients have ARDS.
- Lung protective ventilation with low tidal volume has been shown in the ARDSNET trial to improve mortality and should be initiated early in all patients requiring mechanical ventilation.
- Treatment of specific infections with effective antibiotics is the mainstay of treatment.

Antiretroviral therapy in the ICU

- No prospective studies are available regarding timing of ART in the ICU. Current practice is guided by expert opinion.
- Consultation with an HIV expert and clinical pharmacist is recommended for decisions about initiating, continuing and withholding ART in the ICU.

Continuing ART

- For patients already receiving ART, we generally continue therapy, unless toxicity from the medications is a cause or contributing factor to ICU admission.
- Concerns regarding continuation of ART in ICU involve unpredictable drug absorption from the GI tract due to altered splanchnic blood flow, use of H_2-blockers or proton pump inhibitors, nasogastric feeding, and gastric suctioning which can all lead to sub-therapeutic levels.
- There is a significant potential for adverse drug interactions.
- Poor functional reserve in critically ill patients increases vulnerability to adverse effects of drug reaction and immune reconstitution inflammatory syndrome (IRIS).

Drug interactions

- Antiretroviral agents are metabolized through cytochrome P450 and UGT1A1 enzymes that are responsible for numerous drug interactions.
- Close monitoring for adverse reactions is warranted when ART is administered with the medications listed in Table 48.2.
- Protease inhibitors interact with many classes of drugs and drug interaction should be checked before initiation of any new medication.

Initiation of ART

- Treatment with ART may potentially outweigh risks by improving immune function, thus reducing risk of opportunistic infections and HIV-associated malignancy.
- Certain HIV-associated conditions such as progressive multifocal leukoencephalopathy and HIV-associated thrombotic thrombocytopenic purpura lack disease-specific therapy, and treatment with ART is associated with improved outcomes.

Discontinuing ART

- When treatment is withheld, development of viral resistance and impact on future antiretroviral treatment must be considered.
- HIV resistance genotyping should be performed before restarting ART.

Table 48.2 Medications with significant interactions with antiretroviral medications.

Medication class	Drugs with ART interaction
Cardiac agents	Dronedarone, Amiodarone, Ranolazine
Lipid lowering agents	Lovastatin, Simvastatin
Anti-TB antimicrobials	Rifampin, Rifapentine
Antiepileptic agents	Carbamazepime, Phenobarbital, Phenytoin
Antihepatitis C antiretroviral agents	Boceprevir, Dasabuvir, Ombitasvir, Paritaprevir, Simeprevir
Other agents	Sildenafil, Salmeterol, Ergot derivatives, Cisapride, Alfuzosin.

- Long-term effect of interrupting ART in the non-critical care setting is associated with HIV- and non-HIV-specific disease progression and mortality.
- Overall, the decision to start, continue, or stop ART is complex and involves consideration of a multitude of factors. Consultation with an expert in HIV/AIDS is recommended.

Lactic acidosis in critically ill HIV-infected patients

- Lactic acidosis in HIV-infected patients usually results from hypoperfusion in the setting of critical illness such as sepsis and circulatory shock.
- Lactic acidosis from antiretroviral agents such as didanosine and stavudine was more common in the past. The incidence has decreased with use of newer nucleoside/nucleotide reverse transcriptase inhibitors.
- Lactic acidosis from ART is due to mitochondrial injury. Creatinine clearance of less than 70 mL/min and low CD4 count are risk factors.
- ART should be stopped when lactate >5 mmol/L. An initial lactate level of >9 mmol/L is associated with increased mortality.
- Treatment is supportive with bicarbonate infusion, renal replacement therapy, and mechanical ventilation. Case reports and case series have reported potential benefit of riboflavin, thiamine, and L-carnitine.

Acute kidney injury in HIV

- Acute kidney injury (AKI) is defined as a serum creatinine increase of 50% or 0.3 mg/dL above the baseline creatinine level.
- AKI affects two-thirds of patients admitted to ICU and 32% of these may need renal replacement therapy.
- AKI is associated with increased length of ICU stay and increased mortality.
- Risk factors for AKI include chronic kidney disease, hepatitis C infection, hypertension, and higher severity of illness on admission to ICU.
- HIV-induced nephropathy is characterized by significant proteinuria; renal biopsy may be required for diagnosis. ART may prevent progression to end-stage renal disease (ESRD).
- Nucleoside reverse transcriptase inhibitors (NRTIs) and non-NRTIs require dose adjustment when creatinine clearance is <50 mL/min. Dose adjustment is not required for protease inhibitors.
- Renal replacement therapy should be initiated when appropriate.

Pancreatitis in HIV

- The incidence of acute pancreatitis is increased in HIV-positive patients compared with the general population; incidence varies from 6.1 to 140 per 1000 person-years.
- Lower CD4 count and higher viral loads are associated with increased risk of pancreatitis.
- Medication-induced pancreatitis is still the most common cause of pancreatitis in HIV-infected patients.
- NRTIs associated with pancreatitis such as didanosine and stavudine are seldom used in ART therapy in the USA but their use is still prevalent in resource limited settings.
- Hypertriglyceridemia from protease inhibitors can cause pancreatitis.
- Pentamidine, corticosteroids, ketoconazole, sulfonamides, metronidazole, and isoniazid used in treatment and prophylaxis of opportunistic infections in HIV are associated with pancreatitis.

Table of treatment

Diagnosis	First line treatment	Alternative treatment
PCP	Trimethoprim-sulfamethoxazole for 21 days Prednisone for moderate to severe PCP Days 1–5: 40 mg PO twice daily Days 5–10: 40 mg PO daily Days 11–21: 20 mg PO daily	Pentamidine *Or* Primaquine + clindamycin
Bacterial pneumonia	Antipseudomonal penicillin cephalosporin (cefepime, ceftazidime) *Or* Antipseudomonal carbapenem (imipenem or meropenem) *Or* Lactam/lactamase inhibitor (piperacillin-tazobactam) *Plus* MRSA: linezolid or vancomycin Suspected *Legionella* pneumonia: macrolide or fluoroquinolone	
Bacterial meningitis	Vancomycin *Plus* Third generation cephalosporin *Plus* Ampicillin or penicillin G if *Listeria* infection is suspected	Trimethoprim-sulfamethoxazole, chloramphenicol, meropenem
Cryptococcal meningitis	For induction and consolidation: Amphotericin B IV + flucytosine IV for 2 weeks *Followed by* Fluconazole for minimum of 8 weeks Maintenance: Fluconazole or itraconazole until CD4 >100 and viral load undetectable for 3 months	Liposomal amphotericin B Amphotericin B + fluconazole Fluconazole + flucytosine

Treatment of PCP

- Moderate to severe PCP is defined as :
  - PaO_2 <70 mmHg on room air.
  - Alveolar–arterial gradient ≥35 mmHg on room air.
- Empiric therapy for PCP should be initiated when clinically suspected, before confirmation with bronchoscopy.
- Treatment with corticosteroids for moderate to severe PCP.
- Intravenous methylprednisolone can be substituted for prednisone in mechanically ventilated patients.

Treatment of cryptococcal meningitis

- Elevated CSF pressure is common and lumbar puncture with CSF pressure measurement is warranted.
- If CSF pressure is ≥25 cmH_2O, perform lumbar puncture to decrease pressure by 50% for very high CSF pressures or to <20 cm of CSF.

- If CSF pressure is persistently elevated ≥25 cmH_2O, daily lumbar puncture should be performed until pressure has stabilized for more than 2 days.
- In severe cases resulting in coma, placement of an external ventricular drain may be required to control intracranial pressure.

CLINICAL PEARLS

- Polymicrobial infections and infection with resistant organisms are common in HIV-infected patients. Broad spectrum empiric antibiotics based on clinical presentation should be applied.
- Relative adrenal insufficiency is common in HIV-infected critically ill patients. Empiric corticosteroids should be considered in HIV-infected patients with sepsis and refractory hypotension.
- HIV-infected patients who develop ARDS should be managed with lung protective strategy.

Immune reconstitution inflammatory syndrome in HIV

- IRIS is characterized by a paradoxical worsening of previously diagnosed opportunistic infection (OI) or unmasking of unrecognized OI after initiation of ART.
- The mechanism of IRIS is uncertain.
- It is estimated to occur in 13–16% of patients started on ART and the severity of symptoms varies greatly from mild to life-threatening illness.
- Risk factors for IRIS: starting ART soon after starting treatment for OI, low CD4 count (<100/μL), rapid reduction in HIV RNA viral load after initiation of ART, ritonavir-boosted protease inhibitors or integrase inhibitors.
- Patients with severe IRIS requiring ICU admission present with respiratory failure, visual impairment from retinitis, meningitis, or shock. Respiratory failure is most often associated with PCP and TB.
- IRIS is a diagnosis of exclusion. IRIS associated with PCP can mimic ARDS with fever, hypoxemia, and worsening opacities on CXR. Raised intracranial pressure from tuberculomas or cryptococcal meningitis is associated with increased mortality and morbidity.
- No prospective or randomized clinical trials are available to guide treatment decisions for IRIS in critically ill patients. Non-steroidal anti-inflammatory drugs and corticosteroids can be used to reduce inflammation.
- In severe life-threatening cases of IRIS, ART therapy may be stopped. The decision to continue or stop treatment needs to be individualized and consultation with an HIV/AIDS expert is recommended.
- The potential benefits and risks of starting ART must be considered in a HIV-infected patient with an opportunistic infection to avoid the risk of IRIS.

Prognosis of HIV in the ICU

- Overall ICU mortality of patients with HIV is 15–30%; in-hospital mortality ranges from 30% to 60%.
- Independent predictors of increased mortality are severity of illness based on APACHE II and SOFA scores and requirement for mechanical ventilation and vasopressors.
- PCP pneumonia, PCP-related pneumothorax, acute renal failure, liver cirrhosis, and coma on admission are associated with increased risk of mortality.
- Low CD4 count is not associated with increased mortality.
- Patients receiving highly active ART (HAART) show a trend towards improved survival.

Reading list

Akgün K, Miller R. Critical care in human immunodeficiency virus–infected patients. Semin Respir Crit Care Med 2016;37:303–17.

DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Greenberg J, et al. Outcomes for critically ill patients with HIV and severe sepsis in the era of highly active antiretroviral therapy. J Crit Care 2012;27:51–7.

Huang L, et al. Intensive care of patients with HIV infection. N Engl J Med 2006;355:173–81.

Masur H. Critically ill immunosuppressed host. In: Parrillo J (ed.), Critical Care Medicine: Principles of Diagnosis and Management in the Adult. Philadelphia: Elsevier Saunders, 2019, pp. 901–35.

Perfect JR, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50:7291–1322.

Suggested websites

www.cdc.gov/hiv/policies

Guidelines

National society guidelines

Title	Source	Date and weblink
Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV	Office of AIDS Research Advisory Council (OARAC)	2016 http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
IDSA Practice Guidelines for the Management of Bacterial Meningitis	Infectious Diseases Society of America (IDSA)	2004 http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Bacterial%20Meningitis(1).pdf
IDSA Clinical Practice Guidelines for the Management of Cryptococcal Disease	IDSA	2010 update http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Cryptococcal.pdf

Evidence

Type of evidence	Title and comment	Date and reference
Retrospective cohort study	*Outcomes for Critically Ill Patients with HIV and Severe Sepsis in the Era of Highly Active Antiretroviral Therapy* This study looked at etiology of acute infections in critically ill patients with HIV and factors that affected mortality in the United States in an academic hospital	2012 Greenberg J, et al. J Crit Care 2012;27:51–7
Retrospective study	*Intensive Care of Human Immunodeficiency Virus-infected Patients during the Era of Highly Active Antiretroviral Therapy* Study examining outcomes and use of HAART in critically ill HIV infected patients	2002 Morris A, et al. Am J Respir Crit Care Med 2002;166:262–7

Images

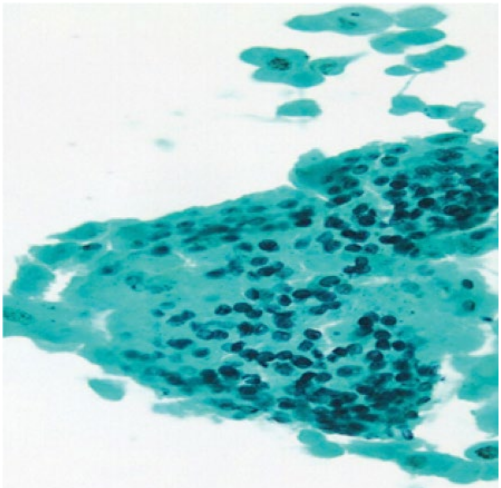

Figure 48.1 GMS stain of bronchoalveolar lavage specimen showing pneumocystis. (See website for color version.)

Figure 48.2 CXR showing bilateral reticulonodular opacities in a patient with PCP.

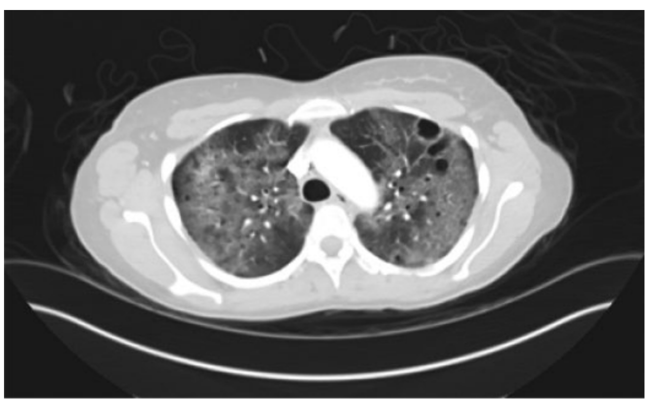

Figure 48.3 CT chest showing bilateral ground opacities characteristic of PCP.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions. The following images are available in color: Figure 48.1.

with website

PART 7

Renal Disorders

Section Editor: Paru Patrawalla

CHAPTER 49

Fluid Resuscitation

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OVERALL BOTTOM LINE

- Indications for fluid resuscitation include a hypovolemic or hypermetabolic state.
- The main systems affecting fluid balance include renin–angiotension, aldosterone, antidiuretic hormone, and natriuretic factors.
- There is no single established standard method for measurement of volume status in the ICU
- The components of total body water include extracellular fluid (ECF) and intracellular fluid (ICF). ECF comprises of plasma volume and interstitial fluid.
- Crystalloids and colloids are used for fluid resuscitation.
- There is evolving literature that some fluids may have organ-protective properties beyond volume expansion alone.
- Complications of fluid resuscitation include volume overload and electrolyte imbalances.

Background

- Fluid resuscitation is the medical practice of replenishing bodily fluid lost through sweating, bleeding, fluid shifts, or other pathologic processes.
- When volume loss occurs, the body reacts by triggering a wide range of physiologic regulatory responses to maintain perfusion in the vascular beds of the vital organs, especially the heart, brain, and kidneys.
- Fluid resuscitation is a crucial component in the management of critically ill patients.

Indications for fluid resuscitation

- Hemorrhage.
- Dehydration.
- Sepsis and shock.
- Insensible losses.
- Fever.
- Open wounds.
- Unhumidified inspired respiratory gases.

Contraindications to fluid resuscitation

- There are no known absolute contraindications, although fluid overload should be avoided because it can exacerbate pulmonary edema and lung injury.
- Concerns exist that fluid resuscitation to a normal blood pressure before controlling bleeding may exacerbate hemorrhage by inhibiting or damaging the formation of clots in areas of vascular injury.
- Additionally, some fears exist regarding replacing volume with fluids that lower the oxygen-carrying capacity of circulating blood.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Factors affecting fluid balance

Three hormones control fluid balance:

- Renin–angiotensin–aldosterone axis.
- Antidiuretic hormone (ADH).
- Natriuretic factors.

Renin–angiotensin–aldosterone axis

- In hypovolemic states, the glomerular filtration rate (GFR) and sodium delivery rate to the distal tubules are relatively low, causing the release of renin as a homeostatic response.
- Renin in turn activates angiotensin I via angiotensinogen which in turn converts to angiotensin II. Angiotensin II plays a key role in aldosterone and ADH release from the adrenal cortex and brain, respectively, which in turn act on the kidney to cause sodium and water retention.
- Renin is a proteolytic enzyme that is released into the circulation primarily by the kidneys. Its release is stimulated by:
  - Sympathetic nerve activation, acting through β_1-adrenoceptors.
  - Renal artery hypotension, caused by systemic hypotension or renal artery stenosis. Decreased sodium delivery to the distal tubules of the kidney.
- Renin cleaves angiotensinogen, to form the decapeptide angiotensin I.
- Vascular endothelium, particularly in the lungs, has angiotensin-converting enzyme (ACE), which cleaves off two amino acids to form the octapeptide, angiotensin II.
- Angiotensin II has several very important functions:
  - Constricts resistance vessels, via angiotensin II (AT_1) receptors, thereby increasing systemic vascular resistance and arterial pressure.
  - Stimulates sodium reabsorption at several renal tubular sites, thereby increasing sodium and water retention by the body.
  - Acts on the adrenal cortex to release *aldosterone*, which in turn acts on the kidneys to increase sodium and fluid retention.
  - Stimulates the release of *vasopressin* (ADH) from the posterior pituitary, which increases fluid retention by the kidneys.
  - Stimulates thirst centers within the brain.
  - Facilitates *norepinephrine* release from *sympathetic nerve* endings and inhibits norepinephrine reuptake by nerve endings, thereby enhancing sympathetic adrenergic function.
  - Stimulates *cardiac hypertrophy* and vascular hypertrophy.

Antidiuretic hormone

- ADH is increased in most critically ill patients, especially those with surgical or traumatic stress. It is also known as arginine vasopressin, a 9-amino-acid peptide made in the supra-ophthalmic nucleus of the hypothalamus.
- The release of ADH is regulated by the osmotic pressure of the blood. Dehydration or increased osmotic pressure of the blood activates ADH release, and activates the V2 receptor, affecting the aquaporin-2 pathway.

Natriuretic factors

- These include atrial natriuretic peptide (ANP), brain natriuretic peptide, and a C-type natriuretic peptide.
- Atrial natriuretic peptide is released from cardiac atrial tissue in response to atrial hypertension (ECF volume overload, heart failure, renal disease, ascites) and primary hyperaldosteronism.
- High levels of ANP increase sodium excretion and increase GFR even in the setting of systemic hypotension.

Distribution of body fluid

- A total of 60% of body weight is composed of water in an average adult male (Figure 49.1).
- The remainder is comprised of 7% minerals, 18% protein, and 15% fat.

- An average adult woman has a total body water content of approximately 50% and slightly increased body fat content.
- The amount of water in different compartments depends entirely on the quantity of solute present in that compartment.
- The addition of solute to any compartment will increase the volume of that compartment by redistribution of water from compartments with lower solute concentrations (i.e. higher water) into the compartment to which the solute was added.

Role of sodium

- Water balance and sodium balance are interdependent.
- Extracellular volume is determined primarily by the sodium content of the body.
- The average serum concentration is 140 mEq/L; intracellular sodium concentration is 12 mEq/L.
- Fluid overload and edema are characterized by excess sodium and water content, whereas hypovolemia is characterized by inadequate sodium content (Figure 49.2).
- A decrease in ECF volume is physiologically different compared with a decrease in effective circulating plasma volume.
- Decreased effective circulating plasma volume may occur with decreased ECF (i.e. hypovolemia) or in the setting of an increased ECF and decreased intravascular oncotic pressure, such as in cases of heart failure, hypoalbuminemia, and inflammatory capillary leak syndromes.
- The combined concentration of solutes in water determines the osmolarity of the fluid, which is the pressure gradient that drives fluid shifts towards equilibration.
  Plasma osmolality (mOsm/kg) = 2[Na] + [glucose]/18 + [BUN]/2.8
  Serum osmolarity (mOsm/kg) = total solute (mOsm)/total body water (kg).
- Different fluid compositions have different effects on plasma and ECF volume.

Impact of 1 L IV fluid on body fluid compartments

Fluid	ICF	ECF	Interstitial	Intravascular
D5W	660 mL	340 mL	226 mL	114 mL
0.95 NaCl	0 mL	1000 mL	660 mL	330 mL

Concept of the third space

- Plasma volume represents the ‘first’ ECF space; the interstitial fluid space is the ‘second’ ECF space.
- The pathologically expanded interstitial fluid space is a ‘third’ ECF space and is expanded primarily at the expense of plasma volume.
- The fluid in the third space is edema fluid and cannot be mobilized by diuresis, dialysis, or fluid restriction.
- This fluid mobilizes spontaneously when inflammation subsides.

Role of water balance

- Water intake is regulated by thirst, triggered by receptors in the anterolateral hypothalamus.
- Critically ill patients cannot communicate thirst, and the thirst mechanism may be dysfunctional in conditions of hypothalamic impairment.

Assessment of fluid status

Physical examination

Signs of hypovolemia include:

- Skin: the skin is cool and clammy, except in the cases of septic shock or ‘warm shock’ in which patients may be febrile. Skin tenting (loss of skin turgor) and dry mucous membranes may be present.

- Cardiac: tachycardia becomes more pronounced with increasing volume loss. Central venous pressure may be low (<5 mmHg). Jugular veins in the neck may not be visible.
- Renal: acute renal failure with decreased urine output.
- Extremities: weak and faint pulses, slow capillary refill, and muscle weakness may be present.
- Neurologic: early findings include altered mental status exhibited by restlessness, agitation, or general CNS depression. Later findings include more severe CNS depression, seizure, or coma.
- Ultrasound: two possible sonographic markers that may be measured at the bedside as surrogates for hypovolemia are the diameters of the inferior vena cava (IVC) and the right ventricle. Complete collapse of the IVC on inspiration in patients with shock is usually an indication of hypovolemia that would respond to fluid resuscitation.

Measurement of cumulative fluid balance

There is no perfectly accurate way to measure daily fluid shifts.

- Nursing daily in/out tallies are helpful but are not always accurate.
- Weight changes reflect total body water changes and not intravascular volume changes.

Management

Rationale for use of fluids
• Correction of reduced circulating ECF volume • Maintenance of cardiac output and organ perfusion • Correction of intracellular water deficits • Treatment of electrolyte abnormalities • Nutrition

- Since hypovolemia is depletion of the volume of the intravascular space, replacement fluid should predominantly fill and remain in the intravascular space.
- Repletion of the total extracellular volume is essential in patients with ECF depletion and intravascular volume will be corrected along with correction of extracellular volume.
- The choice of intravenous fluids should be based on individual patients' needs.
- In clinical practice, the choice of fluid is determined largely by clinician preference, with marked regional variation. No ideal resuscitation fluid exists.

Colloids versus crystalloids

Colloids

- Colloids consist of water, electrolytes, and higher molecular weight proteins or polymers.
- This includes albumin and hydroxyethyl starch.
- Fresh frozen plasma is an expensive and inefficient volume expander and should be reserved for correction of coagulation factor deficiencies.
- Colloids do not offer advantages over crystalloid solutions with respect to hemodynamic effects.
- Albumin is regarded as the reference colloid solution, but its cost limits its use. Although albumin has been determined to be safe for use as a resuscitation fluid in most critically ill patients and may have a role in early sepsis, its use is associated with increased mortality in patients with traumatic brain injury.
- Albumin results in a non-sustainable rise in the colloid oncotic pressure because the plasma albumin level appears to dissipate rapidly. Lung capillary permeability correlates with the severity of acute lung injury or acute respiratory distress syndrome.

Table 49.1 Composition of crystalloid fluids.

	Na^+ (meq/L)	Cl^- (meq/L)	Osm(mosm/L)	Other
0.9% NaCl	154	154	308	
5% Dextrose	154	154	560	Glucose 50 g/L
Ringer's lactate	130	109	273	K^+, Ca^{2+}, lactate
5% Dextrose in water	0	0	252	Glucose 50 g/L
0.45% NS	77	77	154	
5% Dextrose in 0.45% NaCl	77	77	406	Glucose 50 g/L

- Albumin is a hyperoncotic volume expander and can be used to transiently increase the effects of diuretics, such as furosemide, to augment fluid mobilization. This is a common practice known as the 'albumin–furosemide chaser.' However, the utility of this practice is unproven and potentially dangerous.
- The use of hydroxyethyl starch solutions is associated with increased rates of renal replacement therapy and adverse events among patients in the ICU. There is no evidence to recommend the use of other semisynthetic colloid solutions.
- Antibiotics and intravenous albumin, 1.5 g/kg on day 1 and 1 g/kg on day 3, significantly reduced mortality and likelihood of renal failure in patients with cirrhosis and spontaneous bacterial peritonitis.
- Albumin may also be helpful after large volume paracentesis and for correction of dialysis-related hypotension.

Crystalloids

- Crystalloids are made of water and small solutes.
- This includes normal saline, lactated Ringer's solution, and dextrose-containing fluids (Table 49.1).
- Normal saline solution is termed 'normal' because it is isotonic, and only slightly hypertonic at 308 mOsm/L with human ECF. It is acidic and unbuffered.
- Lactated Ringer's solution, or Hartmann's solution, is a buffered or balanced salt solution with a composition that better approximates human ECF. Under normal conditions, the infused lactate is extracted, primarily in the liver, and converted to bicarbonate and water.
- Lactated Ringer's solution is no more effective than normal saline in most clinical situations.
- Large volumes of sodium chloride-containing fluids are likely to cause mild hyperchloremic acidosis. Therefore, some practitioners advocate crystalloid replacement with lactated Ringer's solution, especially in hemorrhagic shock before blood replacement is available.
- Solutions containing only dextrose and water (e.g. 5% dextrose in water) are poor volume replacement solutions because cells rapidly take up the glucose, with water subsequently distributed freely into both the intracellular and extracellular spaces.

Complications of fluid therapy

Volume overload

- Weight gain and weakness are signs of ECF volume overload, which often occurs before edema formation.
- Volume overload leads to pulmonary edema and impairs oxygen diffusion.
- Volume overload can also give way to increased utilization of diuretics, electrolyte imbalances, renal replacement therapy, prolonged mechanical ventilation, and prolonged length of stay.

Hyperchloremic metabolic acidosis due to normal saline

- The implementation of a chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of acute kidney injury and use of renal replacement therapy.

Renal failure

- Patients with severe sepsis assigned to fluid resuscitation with hydroxyethyl starch had an increased risk of death at day 90 and were more likely to require renal replacement therapy, as compared with those receiving Ringer's lactate.

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Images

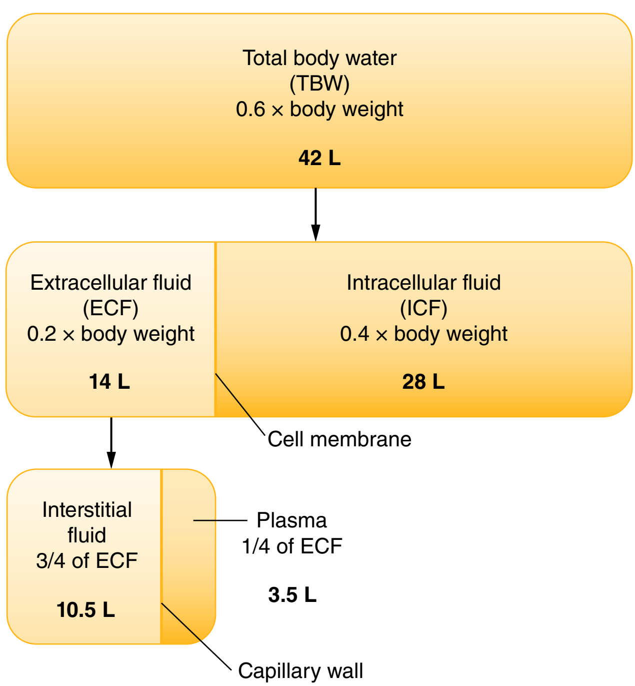

Figure 49.1 Body fluid compartments and distribution of body water.

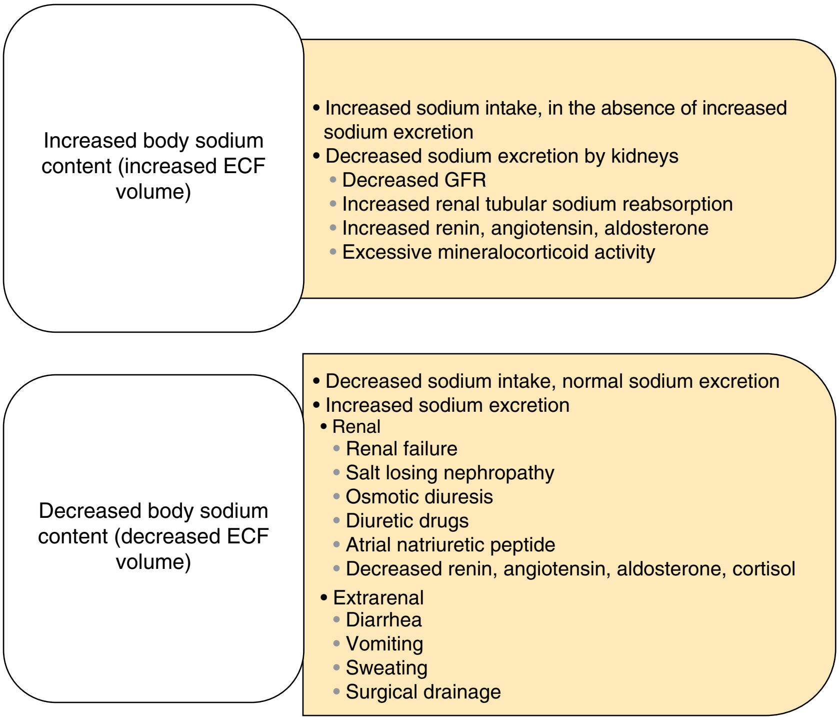

Figure 49.2 Causes of increased or decreased sodium content.

Additional material for this chapter can be found online at: www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 50

Acute Kidney Injury

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OVERALL BOTTOM LINE

- Acute kidney injury (AKI) is common in critically ill patients and is often a complication of an underlying medical condition.
- Early recognition of patients at risk for AKI is essential to minimizing long-term impairment.
- Diagnosis involves a thorough history and physical exam, including bedside ultrasound and medication review.
- Many cases of AKI in the ICU are multifactorial and iatrogenic.

Background

Definition of disease

- AKI is defined as an abrupt decline in kidney function, either reversible or irreversible, associated with retention of metabolic waste products.
- AKI is defined as:
  - Increase in serum creatinine over 48 hours of ≥0.3 mg/dL from baseline, *or*
  - Increase in serum creatinine of >50%, *or*
  - Urine output <0.5 mL/kg/h for more than 6 hours.
- There are two further refined definitions for AKI. The RIFLE and Acute Kidney Injury Network (AKIN) criteria are supported by the Kidney Disease Improving Global Outcomes clinical practice guidelines.

Disease classification

- The RIFLE criteria consist of three grading levels defined as risk, injury, or failure, and two clinical outcomes defined as loss of kidney function and end-stage kidney disease.
- The AKIN criteria are a modification of the RIFLE criteria and include a staging system (Table 50.1).

Incidence/prevalence

- The exact prevalence of AKI in the ICU is limited by varying definitions of AKI and under-reporting based on this limitation. Studies have reported an overall incidence of 20–50%.
- Patients with sepsis have been reported to have a higher incidence of AKI.

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Table 50.1 AKIN and RIFLE criteria for acute kidney injury.

AKIN		RIFLE		Both
Stage	**Serum creatinine or GFR**	**Class**	**Serum creatinine or GFR**	**Urine output**
1	Increase of ≥0.3 mg/dL *or* 1.5–2× baseline	Risk	Creatinine >1.5× baseline or GFR decrease >25%	<0.5 mL/kg/h for at least 6 hours
2	Increase of 2–3× baseline	Injury	Creatinine >2× baseline or GFR decrease >50%	<0.5 mL/kg/h for at least 12 hours
3	Increase >3× baseline *or* ≥4 mg/dL with an acute increase of at least 0.5 mg/dL or newly required renal replacement therapy	Failure	Creatinine >3× baseline or >4 mg/dL with an acute increase of at least 0.5 mg/dL or GFR decrease >75%	<0.3 mL/kg/h for at least 24 hours or anuria for at least 12 hours
		Loss	Persistent loss of kidney function for >4 weeks	
		End-stage renal disease (ESRD)	ESRD >3 months	

Etiology

- AKI has multiple etiologies, further defined based on location of injury as pre-renal, intrinsic, or post-renal.

Pre-renal: due to transient renal hypoperfusion
- Hypotension
- Hypovolemia
- Congestive heart failure with reduced ejection fraction
- Hepatic cirrhosis
- Abdominal compartment syndrome
- Non-steroidal anti-inflammatory drug use

Intrinsic renal
- Tubular: ischemic acute tubular necrosis (ATN), toxic ATN (medication, contrast)
- Vascular/glomerular: thrombotic microangiopathy (hemolytic uremic syndrome, thrombotic thrombocytopenia purpura), glomerulonephritis, atheroembolic, malignant hypertension
- Interstitial: acute interstitial nephritis, pyelonephritis.

Post-renal: obstruction of collecting system
- Urinary tract obstruction: urethral (such as benign prostatic hyperplasia), ureteral

Pathology/pathogenesis

- Pre-renal injury occurs secondary to underperfusion of an otherwise healthy kidney.
- Intrinsic renal injury is caused by disease of the renal parenchyma:
  - Acute tubular necrosis (ATN) is the most common intrinsic cause, and can develop from renal ischemia or injury from endogenous and exogenous substances.
  - Acute interstitial nephritis (AIN) is frequently secondary to one of five etiologies: drug hypersensitivity reaction (most common), infection, immune-mediated, glomerular disease, or idiopathic.
- Post-renal injury occurs in the setting of urinary tract obstruction. Causes of the obstruction can be within the urinary tract itself (clots, stones) or outside the tract (enlarged prostate, tumors, increased surrounding pressures). The increased pressure in the urinary tract alters the pressure gradient at the glomerular capillaries with a resultant decrease in glomerular filtration rate (GFR) and signs and symptoms of AKI.

Prevention

Recognition of high risk patients is key to prevention of AKI. Hospitalized patients, in particular, should have their renal function assessed before any surgical procedures, imaging studies requiring contrast, or administration of any nephrotoxic agents. These patients should also be monitored for any change in urine output from baseline.

Risk factors for acute kidney injury

- Acute on chronic kidney disease (CKD).
- Heart failure.
- Liver disease.
- Diabetes.
- Prior history of AKI.
- Oliguria (<0.5 mL/kg/h).
- Neurologic impairment.
- Hypovolemia.
- Nephrotoxic agent exposure.
- Use of iodinated contrast.
- Symptoms or history of obstruction.
- Age over 65 years.
- Recent chemotherapy.

Primary prevention

- Primary prevention is focused on understanding and responding to the associated risk factor.
- Key components include:
  - Maintaining renal perfusion by correcting for hypovolemia, decreased cardiac output, and sepsis-related vasodilation.
  - Avoiding nephrotoxic agents.
  - Limiting iodinated contrast (especially in diabetic and CKD patients).
  - Ensuring adequate urine output in rhabdomyolysis (>0.5 mL/kg/h).
  - Alkalinizing urine in hyperuricemia.

Causes of intrinsic renal disease

Common causes of ATN	Common causes of AIN
Ischemia (shock state)	Beta-lactam antibiotics
Rhabdomyolysis	Rifampin
Cast nephropathy (myeloma light chains)	Sulfonamides
Aminoglycosides	Fluoroquinolones
Amphotericin B	NSAIDs
Acyclovir IV	Allopurinol
Cisplatin	Proton pump inhibitors
Ethylene glycol	Sarcoidosis
Methanol	Diuretics
Tumor lysis	Aspirin
IV iodinated contrast	Bacterial pyelonephritis
	Viruses (CMV, EBV, HIV, rubeola)

Diagnosis

Typical presentation

AKI generally presents as an increase in serum creatinine on surveillance blood work. This can be associated with a decrease in urine output. Many times, however, patients are asymptomatic, and may be diagnosed incidentally on routine blood work testing.

Clinical diagnosis

History

- Key questions include pertinent prior history and details of the current illness.
- Important past medical history includes prior history of renal dysfunction (acute or chronic), diabetes mellitus, and congestive heart failure.
- Important current information includes NSAID use, decreased oral intake or decreased urine output, difficulty with urination, recent iodinated contrast, and severe volume loss.

Physical examination

The physician should conduct a physical exam directed at possible causes and consequences of AKI.

- Physical exam findings for patients with AKI may include tachycardia, loss of skin turgor, or dry mucous membranes. One can also evaluate for bladder distension by checking for suprapubic tenderness. Flank tenderness could be suggestive of possible pyelonephritis.
- Physical exam findings for sequelae of AKI include assessing volume overload manifested as peripheral edema, pulmonary crackles, and jugular venous distension. Also assess for uremia manifesting as altered mental status, pericardial rub in pericarditis, or distant cardiac sounds in uremic pericardial effusions.
- More invasive exam techniques include measuring bladder pressure through an indwelling urinary catheter in order to assess for abdominal compartment syndrome. Ultrasound can also be used to evaluate for bladder distention.

Laboratory diagnosis

List of diagnostic tests

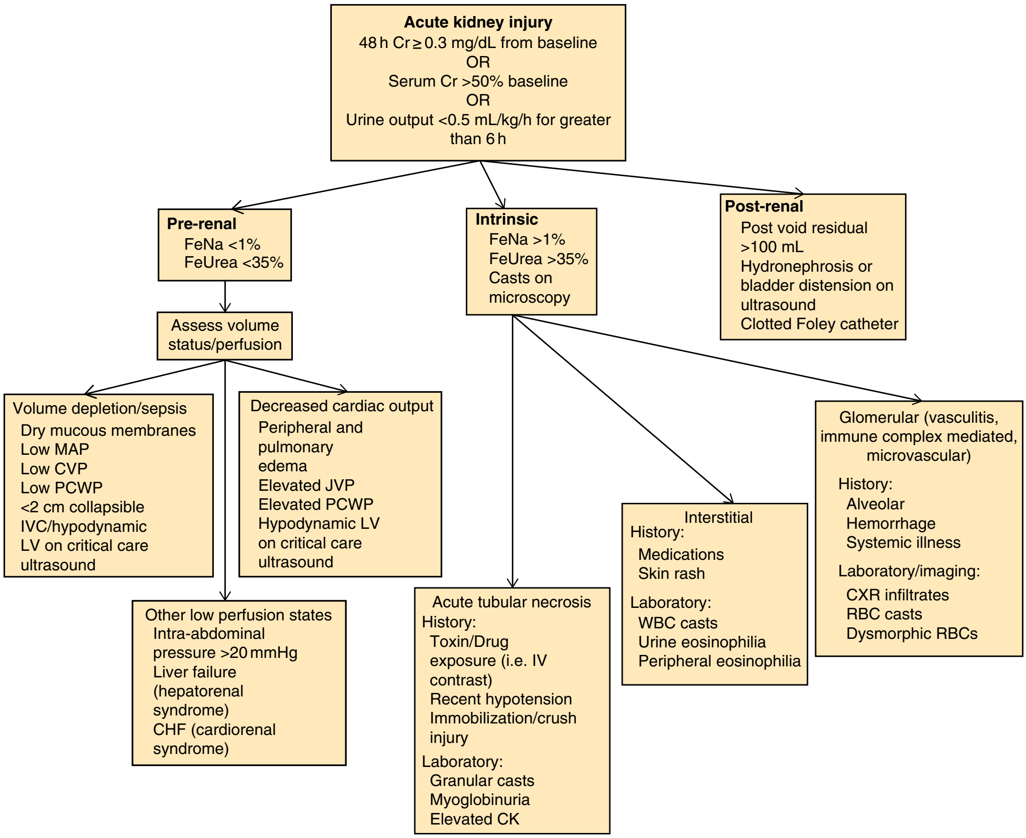
- Initial blood work should include blood urea nitrogen (BUN) and serum creatinine.
- Urine osmolality, urine sodium, urine creatinine, and urine urea are useful to calculate FeNa and FeUrea to help differentiate the location of the injury (pre-renal, intrinsic/ATN) (see Algorithm 50.1).
  - FeNa is <1% in pre-renal injury, reflecting increased reuptake of sodium at the renal tubules. FeNa utility is limited in patients with CKD, early intrinsic injury, and in the elderly.
  - FeUrea has improved sensitivity and specificity in patients taking loop diuretics. A value of <35% suggests pre-renal injury due to renal hypoperfusion.
- Urinalysis is also essential for differentiating between different intrinsic diagnoses and pre-renal AKI.
  - Pre-renal and post-renal AKI: urine sediment is usually bland.
  - Glomerular injury: RBC casts, dysmorphic RBCs.
  - Vascular injury: RBC casts.
  - Tubular injury: muddy brown granular casts, tubular epithelial cells.
  - Interstitial injury: WBC casts (AIN, pyelonephritis), eosinophils (AIN).
  - Urinary tract infection: bacteria, elevated leukocyte esterase.

List of imaging techniques

- A bedside renal and bladder ultrasound provides a safe and easy way to perform modality for detecting urinary obstruction.
- Further imaging for AKI is often not necessary in the initial investigation but can be useful if the cause of the injury is not apparent.
- A CT scan is helpful in diagnosing nephrolithiasis, renal mass, or abscess.

Diagnostic algorithm (Algorithm 50.1)

Algorithm 50.1 Diagnostic algorithm for AKI



Treatment

Treatment rationale

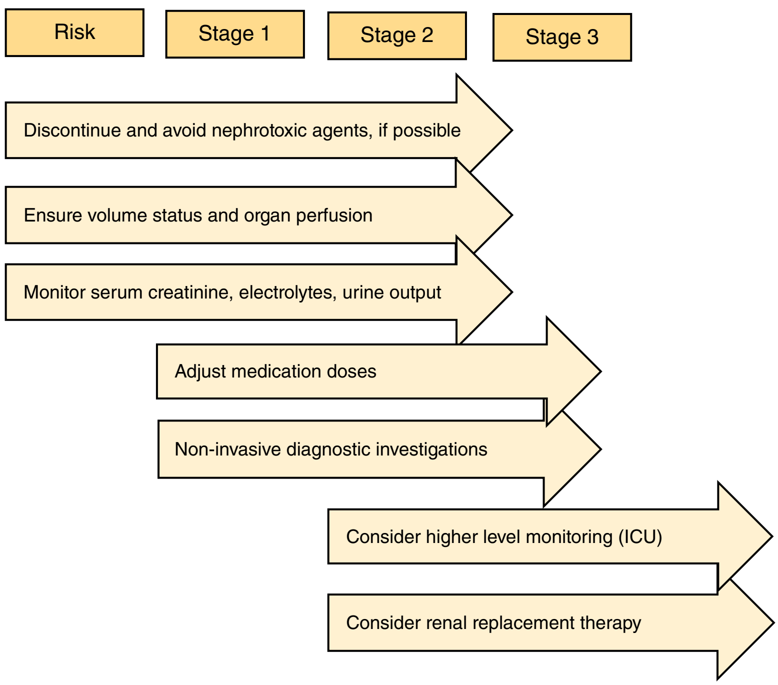
- First line (initial) treatment is supportive care:
  - Adjust or discontinue nephrotoxic medications.
  - Optimize perfusion in patients at risk for kidney injury.
    - Isotonic crystalloids to provide fluid resuscitation in the absence of hemorrhagic shock.
    - Vasopressors as needed in conjunction with volume resuscitation to maintain renal perfusion pressure (i.e. MAP >65 mmHg).
  - Correct metabolic derangements.
  - Escalate management if the severity of AKI progresses from stage 1 to stage 3 (see Algorithm 50.2).
- Dialysis is only indicated for certain conditions:
  - Fluid overload state refractory to diuretics.
  - Hyperkalemia that cannot be readily corrected.
  - Symptoms of uremia (pericarditis, uremic encephalopathy).
  - Severe metabolic acidosis (pH <7.1) refractory to treatment.

Table of treatment

Treatment	Comments
Conservative	Avoid nephrotoxic agents, optimize fluid status, correct metabolic derangements
Medical	Medical diuresis (i.e. loop diuretics) can be useful in fluid overloaded patients with non-oliguric acute kidney injury
Surgical	Foley catheters, ureteral stents, and nephrostomy tubes may be needed in cases of obstructive uropathy causing AKI

Management/treatment algorithm (Algorithm 50.2)

Algorithm 50.2 Management/treatment algorithm of AKI



CLINICAL PEARLS

- Initial management involves correcting volume depletion and maintaining adequate renal perfusion pressure.
- Assessment of obstruction (bladder and kidney ultrasound) and decompression (e.g. Foley catheter, percutaneous nephrostomy tubes) offers rapid reversal of obstructive AKI.
- Renal dosing of all potentially nephrotoxic agents.

Special populations

Pregnancy

- During pregnancy, the GFR increases by approximately 50%, which results in a lower serum creatinine. Thus, normal-appearing levels may in fact reflect an increase compared with baseline.

Elderly

- The elderly are prone to the same etiologies of AKI as the general population. Multiple insults and iatrogenic causes need to be considered.

Others

- Patients with HIV are at an increased risk for developing AKI. In addition to the usual nephrotoxic insults, there is also an increased risk of injury secondary to protease inhibitors.

Prognosis

- The mortality rate for severe AKI is as high as 50%, but the majority of deaths are usually caused by the underlying disease process.
- Half of patients with ATN fully recover, while 40% will have an incomplete recovery. About 5–10% of patients, however, will require maintenance hemodialysis.

Natural history of untreated disease

- A greater degree of kidney injury with decreased urine output is associated with worse outcomes.
- The prognosis is worse in patients undergoing renal replacement therapy.

Reading list

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Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int 2012;81:819–25.

Suggested websites

www.ADQI.net

www.akinet.org

www.kdigo.org

Guidelines

International society guidelines

Title	Source	Date and reference
KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)	Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group Published by the International Society of Nephrology as clinical practice guidelines for acute kidney injury	2017 Kidney International 2017;7:1–59

Additional material for this chapter can be found online at:
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This includes multiple choice questions.

CHAPTER 51

Dialysis

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OVERALL BOTTOM LINE

- Renal replacement therapy (RRT) replaces the function of the failing kidney, resulting in multiple physiologic benefits:
  - Removes excess fluid.
  - Corrects metabolic derangements.
  - Removes uremic toxins, which can produce encephalopathy, coagulopathy, or pericarditis.
  - Corrects electrolyte and acid–base abnormalities (e.g. hyperkalemia).
  - Can be used to treat toxic ingestions of certain drugs.

Background

- The prevalence of acute renal failure requiring RRT in the ICU is 5%.
- There are three main modalities of artificial renal support in the ICU setting: intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and peritoneal dialysis.

Indications for RRT

Absolute indications	Relative indications
Metabolic abnormalities that cannot be controlled with conservative management • Metabolic acidosis (pH <7.1) • Hyperkalemia ($[K^+]$ >6.5 mmol/L or rapidly rising $[K^+]$)	Limited reserve to tolerate consequences of AKI (e.g. advanced CKD)
Complications from uremia (e.g. pericarditis, encephalopathy, coagulopathy)	Anticipated solute burden (e.g. tumor lysis syndrome, rhabdomyolysis)
Volume overload refractory to medical management	Severity of underlying disease, affecting likelihood of recovery of kidney function
Toxicity from dialyzable drug/toxin	

Timing of RRT initiation

The optimal time to initiate RRT in critically ill patients remains uncertain.
There are different guidelines giving recommendations for the timing of initiation of RRT in the ICU (Table 51.1).

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Table 51.1 Guidelines in the USA and UK on when to initiate RRT in the ICU.

Kidney Disease Improving Global Outcomes (KDIGO) Consortium, USA	National Institute for Health and Care Excellence (NICE), UK
Initiate renal replacement therapy (RRT) emergently when life-threatening changes in fluid, electrolyte, and acid–base balance exist Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests – rather than single BUN and creatinine thresholds alone – when making the decision to start RRT	Discuss any potential indications for RRT with a nephrologist, pediatric nephrologist, and/or critical care specialist immediately to ensure that the therapy is started as soon as needed Refer adults, children, and young people immediately for RRT if any of the following are not responding to medical management: • Hyperkalemia • Metabolic acidosis • Complications of uremia (e.g. pericarditis or encephalopathy) • Fluid overload • Pulmonary edema Base the decision to start RRT on the condition of the adult, child, or young person as a whole and not on an isolated urea, creatinine, or potassium value

Benefits of earlier dialysis	Drawbacks of earlier dialysis
Earlier control of metabolic derangements	Iatrogenic episodes of hemodynamic instability that may impede kidney recovery
Earlier control of acid–base derangements	Catheter-associated complications (bleeding, thrombosis, infection, pneumothorax)
Earlier control of uremia	Uncertain clearance of nutrients, trace elements, or vital medications (antibiotics, anticonvulsants)
Earlier management of fluid status/ overload	Exposure to dialysis in patients who would spontaneously recover kidney function without dialysis
Potential beneficial immunomodulation	Increased health care costs

Procedure

Mechanisms of solute transport

- Diffusion: hemodialysis:
  - Small molecular weight solutes move across a semipermeable membrane.
  - Particularly effective for urea, potassium, calcium, and bicarbonate.
  - Clearance decreases rapidly with increasing molecular size.
  - Does not clear protein-bound substances.
- Convection: hemofiltration:
  - Filtration of plasma water across semipermeable membrane as a result of hydrostatic pressure gradient (transmembrane pressure).
  - Amount of solute removed depends on amount of plasma water transported across the membrane and the size of the solute relative to the pore size of the membrane.
  - Effective in the removal of both small and large solutes.
  - Does not clear protein-bound substances.
  - Convection and diffusion can occur simultaneously and as such any distinction is artificial.

- Osmosis:
  - Primarily used for peritoneal dialysis.
  - Glucose solution is used as an osmotic agent (low peritoneal absorption).
- Adsorption: hemoperfusion:
  - Binding of solutes to the hemodiaysis or hemofiltratioin membrane.
  - Charcoal hemoperfusion clears protein-bound compounds.
  - Primarily used for removal of drugs in acute poisoning.

Modes of RRT

Intermittent hemodialysis (IHD)

- IHD is a diffusion-based therapy. Blood is pumped through the compartment of the filter at a higher flow rate than with CRRT techniques, and dialysate is pumped in a counter-current direction at very high flow rates to encourage solute exchange.
- In IHD, solute clearance occurs mainly by diffusion, whereas volume is removed by ultrafiltration.
- Traditionally, intensivists have managed AKI with IHD empirically delivered 3–4 times a week, lasting 3–4 hours per session. The main disadvantage of IHD is the risk of systemic hypotension caused by rapid electrolyte and fluid removal.
- Slow low efficiency daily dialysis is a variant of IHD that is associated with less hypotension; compared with IHD, both blood flow and dialysate rates are substantially slower (100–200 mL/min).

Continuous veno-venous hemodialysis (CVVHD)

- CVVHD is a diffusion-based therapy. Blood is pumped through the blood compartment of the filter and dialysate flows counter-currently (Figure 51.1). The counter-current flow optimizes the diffusion gradient and thus the resulting clearances.
- With CVVHD, dialysate flow is less than the blood flow, corresponding to clearances closely related to dialysate flow.

Continuous veno-venous hemofiltration (CVVH)

- CVVH is a convection-based therapy. Blood is pumped through the blood compartment of the filter and a significant filtrate flow is produced by action of the filtrate pump.
- Filtrate flow requires compensation by infusion of a substitution fluid to the blood flow pre- or post-filter. This way, high filtrate flows can be generated that enhance solute removal.

Continuous veno-venous hemodiafiltration (CVVHDF)

- CVVHDF combines the use of both diffusion and convection therapies. Blood is pumped through the blood compartment of the filter and dialysate flows counter-currently.
- The counter-current flow optimizes the diffusion gradient.
- In addition, a substitution fluid is infused into the blood flow either pre- or post-filter. This is paralleled by filtration of plasma water across the membrane resulting in convective clearance.

Pros and cons of intermittent versus continuous RRT

- There are no definitive data supporting one technique over another, although meta-analyses tend to support potential survival and renal recovery benefit with continuous treatments.
- The optimal mode of RRT depends on the therapeutic aim.
- Continuous therapies may be associated with less hypotension and disequilibrium syndromes (Table 51.2).
- Intermittent therapies mainly rely on diffusion, thus necessitating high dialysate flow rates to maintain high concentration gradients.
- Continuous therapies mainly rely on convection, performed as a low efficiency technique.

Table 51.2 Differences between intermittent and continuous renal replacement therapy.

Intermittent	Continuous
Dialysis monitor (needs sterile substitution fluids)	Simpler hardware
Shorter duration or no anticoagulation	Longer duration of anticoagulation
Relies on diffusion	Relies on convection
Removes [K^+] faster and more effectively	Less efficient
More hypotension and dialysis disequilibrium syndrome from fluid shifts	Less hypotension and dialysis disequilibrium syndrome

- For stable patients, volume and solute removal can be accomplished with intermittent dialysis.
- For unstable patients, continuous therapies can be utilized.
- Slow continuous ultrafiltration can be used in unstable patients who require volume removal.

Anticoagulation during CRRT

- For most patients, CRRT is performed without anticoagulation.
- CRRT may require anticoagulation to prevent clotting of the circuit. Clotting leads to interruption in the time on CRRT and therefore reduction in effectiveness.
- Unfractionated heparin or low molecular weight heparin can be used to prevent clotting in the extracorporeal circuit.
- Regional citrate anticoagulation can be used and has less risk of bleeding. It cannot be used in liver failure or lactic acidosis and patients must be monitored for citrate accumulation.

Complications of RRT

- The most common complications of RRT are hypotension and cardiac arrhythmia.
- Hypotension tends to be more problematic with IHD than with continuous forms of RRT. For this reason CRRT is preferred when patients are hemodynamically unstable.
- In the BEST Kidney Study, new onset or worsening of hypotension complicated RRT in 18% of patients and arrhythmias occurred in 4%.
- Concurrent use of vasopressors and elevated lactate levels increase the risk of dangerous arrhythmias during RRT.

Management of complications (Table 51.3)

- Use bicarbonate dialysate to correct acidosis for prevention of arrhythmias.
- Maintain potassium and calcium at appropriate levels.
- Use of dialysate with potassium <2 mmol/L should be avoided.

Prognois

Prognosis for treated patients

- Overall hospital mortality of ICU patients with AKI requiring dialysis ranges from 40% to 60%.
- Among survivors, dialysis dependence at hospital discharge is about 14%.
- There are a paucity of data indicating superiority between intermittent and continuous modalities with regard to long-term outcome:
  - Mortality is similar in both intermittent and continuous modalities.
  - No evidence-based guidelines exist for selecting CRRT versus IHD with regard to residual renal function recovery.

Table 51.3 Causes and treatment of complications of RRT.

Complication	Etiology	Management
Hypotension	Intravascular volume depletion Antihypertensive/nitrates prior to dialysis Allergic reaction to dialyzer Left ventricular dysfunction Autonomic dysfunction Others: myocardial infarction, sepsis, cardiac tamponade, bleeding	Infusion of normal saline Reduction of ultrafiltration rate
Active bleeding/ coagulopathy	Exacerbated by anticoagulation Platelet dysfunction from uremia	Minimize or hold heparin dosage IV desmopressin (0.3 μg/kg in 50 mL saline every 4–8 hours), IV conjugated estrogen (0.6 mg/kg/ day for 5 days), or intranasal desmopressin
Clotting of the extracorporeal circuit during dialysis	Air in circuit or poor priming of heparin line Inadequate blood flow caused by needle or catheter positioning Clotting Frequent blood flow interruptions	Heparin dose adjustment ± Vascular access revision
Dialysis-associated steal syndrome	Arteriovenous fistula results in reduced blood flow to hand	Severe symptoms: surgical or radiologic revision Mild symptoms: improve with time
Dialysis-associated pericarditis	Dialysis associated (different from uremic pericarditis)	Intensification of dialysis to 6–7 times/week Minimize or discontinue anticoagulation Treatment failure or evidence of tamponade: pericardiectomy
Dialysis disequilibrium	Occurs in first few treatments More common in profoundly uremic patients Due to CNS edema from rapid osmolar shifts Symptoms: nausea, emesis, headache, confusion, seizures	Lower blood flows and shorter treatment duration during initial sessions
Anaphylactic and anaphylactoid reactions	Anaphylaxis: IgE mediated Anaphylactoid: release of mast cell mediators Usually ~5–20 minutes into hemodialysis Drug induced (e.g. iron dextran) Bradykinin-mediated reactions	Stop hemodialysis without return of extracorporeal blood to patient Epinephrine, antihistamines, corticosteroids, respiratory support Using gamma ray or steamed filters may prevent hypotension (first use) Mild symptoms (e.g. chest/back pain) (20–40 minutes into hemodialysis) may improve over time and hemodialysis does not need to be stopped
Fever and pyrogenic reactions	Water or bicarbonate dialysate Improperly sterilized dialyzers Use of central venous dialysis catheters Cannulation of infected arteriovenous grafts or fistulae	If hemodynamically unstable, hold dialysis and initiate supportive measures (vasopressor, fluid bolus) Infectious work up (e.g. catheter sites or arteriovenous graft) Prompt use of antibiotics

Follow-up tests and monitoring

- Drug clearance increases with RRT. Monitor drug levels (e.g. antibiotics, anticonvulsants) to ensure adequate therapeutic levels.
- Continuous modalities require the patient to be bedbound, and thus will need vigilant nursing protocols to prevent pressure ulcers.

Reasons for discontinuation of RRT in the ICU

There are a paucity of data on optimal timing for discontinuation but the following are reasons for stopping RRT in the ICU:

- Increase in urine output is the most common determinant of kidney function recovery and thus successful weaning from dialysis.
- Decrease in BUN and creatinine.
- Improved metabolic state.
- Improved fluid overload.
- Withdrawal of therapy.

Reading list

Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis 2004;44:1000–7.

Bellomo R, Ronco C. An introduction to continuous renal replacement therapy. In: Bellomo R, Baldwin I, Ronco C, Golper G (eds), Atlas of Hemofiltration. London: Bailliere Tindall, 2001, pp. 1–9.

Oudemans-van Straaten HM, et al. (eds) Acute Nephrology for the Critical Care Physician. New York: Springer, 2015.

Uchino S, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of prospective multicenter observational study. Crit Care Med 2009;37:2576–82.

Uchino S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294(7):813–18.

Vinsonneau DCC, et al. A prospective, multicentre, randomized clinical trial comparing continuous venovenous hemodiafiltration to intermittent hemodialysis for the treatment of acute renal failure in intensive care unit patients with multiple organ dysfunction syndrome. Lancet 2006;368:379–85.

Suggested websites

www.adqi.net
www.akinet.org
http://www.cdc.gov/dialysis/patient/
www.crrtonline.com
www.ispd.org/lang-en/treatmentguidelines/guidelines
www.ncepod.org.uk

Image

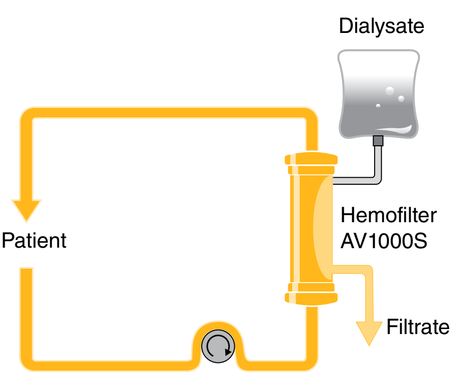

Figure 51.1 Continuous veno-venous hemodialysis (CVVHD) circuit. The dialysate runs in a counter-current to blood flow within the hemofilter chamber, promoting solute exchange.

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 52

Electrolyte Disorders

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OVERALL BOTTOM LINE
- Electrolyte disorders are common in the ICU.
- Severe hyperkalemia is a life-threatening disorder, requiring immediate therapy.
- Disorders of sodium reflect water excess or loss.

Hyperkalemia

BOTTOM LINE
- Hyperkalemia is usually caused by either increased potassium release from cells or impaired urinary clearance of potassium.
- In patients with ECG changes or a very high or rapidly rising potassium level, treatment should be initiated.
- Treatment revolves around temporizing rapidly acting therapies and definitive therapies for potassium removal from the body.

Background

Definition of disease
- Hyperkalemia is defined as a serum potassium level that is above the upper limit of normal (usually 5.0–5.2 mmol/L).

Incidence/prevalence
- The prevalence of hyperkalemia in hospitalized patients has been reported to be between 1% and 10%.

Etiology
- The etiology of hyperkalemia can be broken down into causes due to potassium release and causes due to impaired renal excretion of potassium.
- Excessive potassium release can be due to phlebotomy, hyperosmolality, acidosis, direct tissue injury, or drugs.
- Renal causes of hyperkalemia include renal insufficiency, reduced aldosterone secretion or response, and reduced effective arterial blood volume.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Predictive/risk factors

Risk factor	Odds ratio
Use of ACE inhibitor or angiotensin receptor blocker	2.2
Use of trimethoprim/sulfamethoxazole (TMP-SMX)	5.1

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Low potassium diet.
- Avoid periods of fasting without parenteral insulin administration.
- Avoid medications that are known to cause hyperkalemia.

Diagnosis

- Obtain thorough medication history.
- Assess for muscle weakness, especially in the lower extremities.
- Auscultate for cardiac arrhythmias.
- Obtain serum potassium and magnesium concentrations as well as renal function.
- Obtain a 12-lead ECG.

Differential diagnosis

Differential diagnosis	Features
Guillain–Barré syndrome	Respiratory and cranial nerve involvement are rare in hyperkalemia
Spinal cord compression	Cord compression will have an abnormal sensory exam and bowel/bladder dysfunction

Clinical diagnosis

History

- The clinician should inquire about typical manifestations of hyperkalemia such as muscle weakness and palpitations and investigate medication use that may cause renal insufficiency or hyperkalemia.

Physical examination

- Physical examination is often unremarkable in patients with hyperkalemia but in severe cases can reveal ascending muscle weakness or an irregular heart rhythm.
- Diminished or absent deep tendon reflexes can be present.
- Physical manifestations of renal failure such as altered mental status, uremic frost, and edema can be encountered. If signs of trauma or prolonged immobility are found, rhabdomyolysis can be suspected as a cause of hyperkalemia.

Disease severity classification

- Mild hyperkalemia: serum potassium 5.5–6 mmol/L.
- Moderate hyperkalemia: serum potassium ≥6 mmol/L.
- Severe hyperkalemia: serum potassium ≥6.5 mmol/L.

Laboratory diagnosis

- Serum potassium, BUN, and creatinine levels for degree of hyperkalemia and renal failure.
- Urinalysis for causes of renal insufficiency.
- Glucose level to evaluate for diabetes mellitus.
- Blood gas for presence and degree of acidosis.
- Calcium level to evaluate for hypocalcemia which can lead to arrhythmias.
- Digoxin level to assess for digitalis toxicity as an etiology for electrolyte disturbance.
- Serum cortisol and aldosterone levels to assess for mineralocorticoid insufficiency as a cause for hyperkalemia.
- Electrocardiogram for potentially life-threatening arrhythmias and for early changes of hyperkalemia such as peaked T-waves, short QT interval, and depression of the ST segment.

Potential pitfalls/common errors made regarding diagnosis of disease

- A hemolyzed sample can falsely elevate the potassium level.
- Repeated fist clenches can falsely elevate potassium levels.
- Prolonged storage of serum sample can lead to pseudohyperkalemia.
- Extremely high leukocyte or platelet counts can lead to pseudohyperkalemia.

Treatment

Treatment rationale

- For mild hyperkalemia (5.5–6 mmol/L), remove potassium with potassium exchange resins (sodium zirconium cyclosilicate 10g PO), diuretics (furosemide 1 mg/kg IV), or dialysis.
- For moderate hyperkalemia (≥6 mmol/L), use above strategies *and* shift potassium into cells with insulin (10 units IV) and dextrose (50 g IV).
- For severe hyperkalemia (≥6.5 mmol/L) without ECG changes, use above strategies *and* add albuterol (5 mg inhaled, may repeat) and sodium bicarbonate (50 mmol IV).
- For severe hyperkalemia (≥6.5 mmol/L) with ECG changes, use above strategies but *first* stabilize the myocardial cell membrane with calcium chloride (10 mL IV of 10% solution).

CLINICAL PEARLS

- Use temporizing measures when hyperkalemia is moderate or severe.
- Stabilize the cardiac membrane when ECG changes are present.
- Only exchange resins, diuresis, or dialysis will be definitive treatments.

Special populations

In postoperative patients, who are at a presumed risk for ileus, sodium polystyrene sulfate has been reported to cause intestinal necrosis and should be avoided in this population. This also applies to patients with obstructive bowel disease.

Prognosis

Natural history of untreated disease

- Untreated, the ECG will evolve with worsening hyperkalemia:
  - Early changes include peaked T-waves, short QT, and depression of the ST segment.
  - This will evolve into bundle branch blocks, prolonged PR, and smaller P-waves which will eventually disappear.
  - The QRS complex will widen to form a sine wave.
  - Ventricular fibrillation or asystole will eventually result.

Prognosis for treated patients

- All changes will reverse with treatment of the hyperkalemia.

Hypokalemia

BOTTOM LINE

- Hypokalemia is usually caused by a shift of potassium into cells, by hypomagnesemia, or by gastrointestinal or urinary losses.
- In patients with high risk for arrhythmias, or those experiencing signs or symptoms of hypokalemia, treatment should be initiated.
- Treatment revolves around identifying the cause of the hypokalemia and repleting the potassium.

Background

Definition of hypokalemia

- Hypokalemia is defined as a serum potassium level that is below the lower limit of normal (usually 3.5–3.6 mmol/L).

Incidence/prevalence

- Hypokalemia occurs in up to 21% of hospitalized patients.
- Hypokalemia occurs in up to 2–3% of outpatients.

Etiology

- Causes of hypokalemia can be divided into abnormal losses, transcellular shifts, and inadequate intake.
- Abnormal losses can be due to medications, gastrointestinal losses, urinary losses, hypomagnesemia, and hemodialysis.
- Transcellular shifts can be due to medications, refeeding syndrome, adrenergic stimulation, alkalosis, or thyrotoxicosis.

Predictive/risk factors

Risk factor	Odds ratio
Age	1.3 for each decade
Parenteral loop diuretics	2.3

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- A history of diuretic use or diarrhea should prompt suspicion for hypokalemia.
- Symptoms can include generalized weakness, ascending paralysis, or palpitations.
- An electrocardiogram should be performed to assess for changes related to hypokalemia.
- A metabolic profile, including glucose and magnesium levels, should be obtained to confirm the diagnosis.
- Urine creatinine and electrolytes can be helpful in certain situations.

Clinical diagnosis

History

- The clinician should inquire about typical manifestations of hypokalemia such as muscle weakness and palpitations and investigate the medications that are known to cause hypokalemia.
- Inquire about gastrointestinal symptoms such as vomiting or diarrhea.

Physical examination

- A physical examination is often unremarkable in patients with hypokalemia but in severe cases can reveal flaccid muscle weakness or an irregular heart rhythm.
- Check blood pressure as hypertension can be a clue to hyperaldosteronism or Cushing's syndrome.
- Assess respirations, as Kussmaul breathing can be present in diabetic ketoacidosis.

Disease severity classification

- Mild hypokalemia: serum potassium 3–3.5 mmol/L.
- Moderate hypokalemia: serum potassium 2.5–3 mmol/L.
- Severe hypokalemia: serum potassium <2.5 mmol/L.

Laboratory diagnosis

- For mild hypokalemia with an evident cause, no further investigation is necessary.
- For unclear causes or more severe hypokalemia, a full chemistry panel including magnesium level should be obtained. Consideration should be given to obtaining an arterial blood gas.
- If cause remains unclear, assessing urinary excretion of potassium can be helpful. Urine potassium, osmolality, and creatinine levels as well as plasma osmolality levels should be added to the diagnostic investigations.
- If a cause remains elusive, a plasma aldosterone : renin ratio should be obtained to rule out primary hyperaldosteronism, especially in the setting of hypertension. A dexamethasone suppression test should be considered to rule out Cushing's syndrome, especially with typical clinical features of steroid excess. Serum TSH and thyroxine should be obtained to rule out thyrotoxic periodic paralysis.
- Under the care of a specialist, adrenal imaging will sometimes be indicated to assess for congenital adrenal hyperplasia.
- Under the care of a specialist, duplex ultrasonography or renal artery angiography may be indicated to assess for renal artery stenosis.

Treatment

Treatment rationale

- In the presence of hypomagnesemia, magnesium should first be repleted.
- Once hypokalemia is identified, its cause should be investigated. In the meantime, potassium should be repleted.
- In the setting of hypophosphatemia, such as with diabetic ketoacidosis or Fanconi's syndrome, potassium phosphate can be used as repletion.
- In the setting of metabolic acidosis, potassium bicarbonate or one of its precursors (acetate or citrate) can be used to balance the pH.
- In almost all other settings, potassium chloride should be used since there is often an element of metabolic alkalosis with most causes of hypokalemia.

Table of treatment

Treatment	Comments
Conservative	Suitable for patients with no clinical manifestations and mild hypokalemia
Medical	Potassium chloride 40 mEq IV/PO Potassium phosphate 1 mmol/kg IV Potassium citrate 10 mEq PO three times daily Potassium acetate 40 mEq IV

Prevention/management of complications

- Prevention of hypokalemia in patients at high risk (e.g. patients receiving chronic diuretics) includes regular potassium supplementation in the form of potassium chloride or providing a list of high potassium foods to supplement the diet.

CLINICAL PEARLS

- Potassium-sparing diuretics should be considered in cases of chronic diuretics, Gitelman's syndrome, or Bartter's syndrome as it can prove more effective in preventing hypokalemia.
- Potassium-sparing diuretics should be used as first line agents in patients with primary hyperaldosteronism.
- If pain or phlebitis occurs in a peripheral vein due to potassium infusion, decrease the concentration or the rate of infusion.

Prognosis

- In patients with hypertension, potassium levels less than 3.5 have been associated with a hazard ratio of 2.8 for 90 day mortality, when correcting for covariates.

Hyperphosphatemia

BOTTOM LINE

- Hyperphosphatemia occurs due to an endogenous or exogenous phosphate load or due to impaired renal function.
- When associated with hypocalcemia, hyperphosphatemia can be life threatening and can be treated by saline infusion or hemodialysis.

Background

Incidence/prevalence

- The prevalence of hyperphosphatemia is low in patients without renal disease.
- Hyperphosphatemia has been reported to occur in almost 70% of patients on chronic hemodialysis.

Etiology

- Increased phosphate load.
- Renal dysfunction.
- Shift of phosphate into the extracellular space.
- Tumor lysis syndrome.

Pathology/pathogenesis

- Hyperphosphatemia causes symptoms due to calcium phosphate crystals forming in the blood leading to symptoms of hypocalcemia.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Limiting dietary phosphate can prevent hyperphosphatemia.
- Administration of phosphate binders can prevent hyperphosphatemia.
- Vitamin D supplementation improves parathyroid hormone (PTH) levels.

Primary prevention

- Limiting dietary phosphate can be helpful even in early chronic kidney disease.
- Trending tubular reabsorption of phosphate (TRP) can he be helpful in deciding when to initiate phosphate-lowering therapies (see later).
- Phosphate binders can be used in the prevention of hyperphosphatemia.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Almost all patients with hyperphosphatemia will carry a diagnosis of chronic kidney disease.
- Examination findings may show evidence of hypocalcemia such as tetany and cardiac rhythm disturbances.
- Hyperphosphatemia is confirmed by measuring serum phosphate levels.

Typical presentation

- A typical presentation of hyperphosphatemia will be a patient with either acute or chronic renal dysfunction who was found on blood tests to have elevated phosphate levels.

Clinical diagnosis

History

- In taking a history, the clinician should inquire about common medications that contain phosphate (such as phosphate enemas and fosphenytoin).
- If the patient was immobile or crushed, attention should be paid to rhabdomyolysis as a potential cause for the phosphate disturbance.
- In a patient with a history of recent chemotherapy, tumor lysis syndrome should be on the differential.
- Otherwise, other causes of renal failure should be elucidated, as this is the most common scenario for a presentation of hyperphosphatemia.

Physical examination

- The physical exam should focus on clinical manifestations of hypocalcemia, which often accompanies hyperphosphatemia. Assessing muscle twitching, spasms, as well as extrapyramidal signs and parkinsonism can all be useful in the physical exam.

Useful clinical decision rules and calculators

- TRP can be determined by calculating the ratio of phosphate clearance to creatinine clearance as follows: $\%TRP = 1 - [(U_P/P_P) \times (P_{Cr}/U_{Cr})] \times 100$, where U_P and P_P are plasma and urine phosphate and U_{Cr} and P_{Cr} are plasma and urine creatinine.
- When TRP falls below normal (<80), it may be beneficial to initiate interventions to limit phosphate retention and avoid the ensuing elevation of serum phosphorus.

Laboratory diagnosis

- Serum phosphate, urea nitrogen, creatinine, calcium, and remainder of electrolytes are helpful.
- Urine phosphate, creatinine, and remainder of urine electrolytes are helpful for TRP calculation.

Potential pitfalls/common errors made regarding diagnosis of disease

- A falsely elevated phosphate level can be encountered in cases of hyperglobulinemia, hyperlipidemia, hemolysis, and hyperbilirubinemia.
- Administration of liposomal amphotericin B can also lead to pseudohyperphosphatemia.

Treatment

Treatment rationale

- Treatment of acute hyperphosphatemia usually revolves around treatment of the associated hypocalcemia.
- Treatment of chronic hyperphosphatemia most often occurs in patients with renal dysfunction and revolves around dietary phosphate restriction (<900 mg/day) and phosphate binder therapy to decrease intestinal absorption.
- Phosphate binder therapy is primarily chosen based on calcium status. Hypercalcemic patients should take non-calcium-containing binders such as sevelamer or lanthanum while hypocalcemic or normocalcemic patients should take calcium-containing binders such as calcium acetate or calcium carbonate.
- Longer or more frequent dialysis sessions can be useful for refractory hyperphosphatemia in patients who are dialysis dependent.

Table of treatment

Treatment	Comments
Conservative	Dietary phosphate restriction for patients with chronic kidney disease
Medical	Phosphate binders: Calcium acetate 1334 mg with each meal Sevelamer 800–1600 mg with each meal Lanthanum 500 mg with each meal
Other	Prolonged or more frequent hemodialysis sessions

CLINICAL PEARLS

- Always assess calcium levels prior to decision on the treatment method for hyperphosphatemia.

Hypophosphatemia

BOTTOM LINE
- Hypophosphatemia occurs due to decreased absorption of phosphate, increased urinary or dialysis excretion of phosphate, or redistribution of phosphate into the intracellular space.
- Phosphate depletion can cause low levels of ATP leading to a decrease in myocardial contractility, diaphragm strength, and mental status. Early administration of oral or IV phosphate solutions is paramount.

Background

Incidence/prevalence
- The prevalence of hypophosphatemia depends on the definition of the lower range of normal and the population being studied.
- Hypophosphatemia has been reported to occur in 3% of hospitalized patients and up to 80% of patients with sepsis.

Etiology
- Decreased absorption of phosphate.
- Increased excretion of phosphate.
- Shift of phosphate to the intracellular space.

Pathology/pathogenesis
- Hypophosphatemia causes symptoms due to depletion of intracellular ATP and 2,3-DPG. Symptoms usually will not develop unless levels are below 1 mg/dL. Depletion below this level will affect the musculoskeletal, cardiovascular, pulmonary, neurologic, and hematologic systems.

Predictive/risk factors

Risk factor	Odds ratio
Acute respiratory disease	3.2
Use of dopamine	8.7
Malnutrition	4.0

Prevention
- Treating electrolyte abnormalities prior to initiating feeding in malnourished patients may decrease complications related to refeeding syndrome.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS
- In taking a history, screen for patients with conditions known to cause hypophosphatemia such as diabetic ketoacidosis, alcoholism, anorexia nervosa, and vomiting or diarrhea.
- Exam findings may show weakness, arrhythmias, respiratory failure, and encephalopathy.
- Hypophosphatemia is confirmed by measuring serum phosphate levels.

Typical presentation

- A typical presentation of hypophosphatemia will be in a patient who was administered glucose with concomitant release or administration of insulin who was found on blood tests to have decreased phosphate levels.

Clinical diagnosis

History

- While taking a history, focus on medications that may cause shift of phosphate into the intracellular space such as beta-agonists, epinephrine, dopamine, insulin, glucagon, steroids, and xanthine derivatives.
- Attention should be paid to processes that may decrease intestinal absorption such as vomiting, diarrhea, and phosphate binders as well as processes that increase urinary excretion of phosphate such as diuretics, hyperparathyroidism, vitamin D deficiency, and kidney transplantation.

Physical examination

- The physical exam should focus on clinical manifestations of hypophosphatemia such as weakness (including diaphragmatic weakness), congestive heart failure, arrhythmias, encephalopathy, and seizures.

Useful clinical decision rules and calculators

- Fractional excretion of phosphate: $FePO_4 = [U_{PO_4} \times P_{Cr} \times 100] / [P_{PO_4} \times U_{Cr}]$

Disease severity classification

- Moderate hypophosphatemia: 1.0–2.5 mg/dL.
- Severe hypophosphatemia: <1.0 mg/dL.

Laboratory diagnosis

- Serum phosphate, urea nitrogen, creatinine, calcium, and remainder of electrolytes are helpful.
- Urine phosphate, creatinine, and remainder of urine electrolytes are helpful for $FePO_4$ calculation.
- $FePO_4$ <5% indicates the kidneys are appropriately excreting low amounts of phosphate and the cause is related to intracellular shift or decreased intestinal absorption.
- $FePO_4$ >5% indicates renal phosphate wasting.

Treatment

Treatment rationale

- Treatment of hypophosphatemia should be based on the level of phosphate and if the patient is symptomatic.
- With moderate hypophosphatemia, oral replacement (1000 mg/day) should be initiated.
- If the patient is on a ventilator or hypophosphatemia is severe, then intravenous therapy (0.08–0.16 mmol/kg) should be initiated.

Table of treatment

Treatment	Comments
Conservative	Discontinue offending medications
Medical	Phosphate replacement: • NaPhos 2.5–5.0 mg/kg twice or three times daily • KPhos 0.15–0.3 mmol/kg as an IV solution to infuse over 12 hours; repeat as needed

Prevention/management of complications

- Monitor phosphate levels while on phosphate repletion as overcorrection can occur with reversal of the underlying cause.

> **CLINICAL PEARLS**
> - Always assess symptoms prior to deciding on treatment as symptoms can be vague and non-specific.

Special populations

When repleting phosphate, patients with a reduced glomerular filtration rate should receive approximately one-half of the suggested initial dose.

Hyponatremia

> **BOTTOM LINE**
> - Hyponatremia is a problem of water in excess of sodium in the serum, and is usually due to excess secretion of antidiuretic hormone (ADH) which may be appropriate or pathologic.
> - Hyponatremia may be driven by impaired renal function, or the physiologic limit of normal renal function.
> - Correction of the physiologic causes for increased ADH secretion along with controlled replacement of the sodium deficit is the mainstay of treatment.
> - The syndrome of inappropriate ADH secretion (SIADH) is a discrete entity with identifiable underlying causes, and is treated as such.

Background

Definition of disease

- Hyponatremia is defined by a serum sodium <135 mEq/L.
- A serum sodium <125 mEq/L is generally defined as severe hyponatremia.
- Neurologic sequelae often occur at a serum sodium <115 mEq/L.

Incidence/prevalence

- A serum sodium <130 mEq/L is seen in 1–4% of hospitalized patients.
- A fraction of these patients have hyponatremia due to SIADH.

Etiology

- Hypovolemia with unsuppressed ADH secretion or due to diuretics.
- Hypervolemia with decreased effective arterial perfusion (CHF, cirrhosis), causing unsuppressed ADH secretion.
- Water intake in excess of the renal concentrating ability (psychogenic polydipsia).
- Primary unregulated and inappropriate secretion of ADH (SIADH).
- Hyponatremia can also occur in other disease states such as cerebral salt wasting.

Pathophysiology

- ADH, which promotes free water retention, normally falls as serum osmolality falls, and as a result promotes the excretion of water to maintain serum sodium concentration.

- This relationship may be impaired in certain disease states or in the setting of physiologic stressors wherein the actual, effective, or 'anticipated' intravascular volume status is decreased. In these cases, ADH levels remain high despite decreasing serum osmolality, and hyponatremia ensues due to free water retention.
- In patients with polydipsia, intake of water exceeds the physiologic ability of the kidneys to excrete free water over a given amount of solute intake.
- In SIADH, an unregulated secretion of ADH occurs despite euvolemia, causing free water retention and hyponatremia.

Predictive/risk factors

- Hypovolemia due to nausea, vomiting, diarrhea, burns, trauma, pain, or diuresis.
- Hypervolemia with decreased effective arterial volume, such as with cirrhosis and congestive heart failure.
- SIADH can be seen in pulmonary malignancy and infections, adrenal insufficiency, meningitis, and with the use of selective serotonin reuptake inhibitors (SSRIs).

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Monitor volume status (input/output, daily weights) in at-risk patients.
- Avoid hypotonic fluids (e.g. D5W or 0.45% saline).
- Treat stimuli of inappropriate ADH secretion, e.g. pain, nausea, hypovolemia.
- Manage underlying disease states, e.g. malignancy, infection, adrenal insufficiency.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Initial labs should include a serum sodium and osmolality, and a urine sodium and osmolality.
- Additional labs should include a urine specific gravity, a urine potassium level, and a urine urea level.
- Clinical assessment of volume status is the first step to diagnosis, followed by an assessment of appropriate renal reabsorption of sodium.
- Calculation of the Adrogue–Madias formula (http://www.medcalc.com/sodium.html) may help in the management of hyponatremia. This formula indicates the specific crystalloid formulation and rate of infusion required to correct the sodium level from a baseline to a desired target level over a given period of time.
- SIADH should be diagnosed in the appropriate clinical context. In a euvolemic patient, with a urine osmolality greater than the serum osmolality, this involves demonstrating an inappropriately concentrated solute excretion. Often SIADH is present along with another cause for hyponatremia.

Typical presentation

- Patients with hyponatremia often come to medical attention for other complaints, and are found to have hyponatremia in their initial investigations. These patients may come to the attention of an intensivist when the initial management of hyponatremia becomes complicated, or when the patient develops neurologic signs and symptoms.

Clinical diagnosis

History

- Laboratory error or pseudohyponatremia should first be excluded.
- History of comorbid conditions such as CHF, cirrhosis, cancer, or infection should be elicited.

- Use of thiazide diuretics, SSRIs, mannitol, and IVIg should be determined and held if possible.
- A history including an estimation of solute and water intake, and the chronicity of symptoms and previous sodium levels, is often helpful.
- At the time an intensivist encounters a patient, previous volume resuscitation measures must be taken into account.
- Subtle or overt neurologic signs as well as urinary complaints and procedures (e.g. transurethral resection of the prostate) must be considered.

Physical examination

- Neurologic signs and symptoms should be evaluated. Overt seizures are an uncommon but concerning finding.
- Signs of hypothyroidism and adrenal insufficiency (weight changes, hyperpigmentation) are often subtle, but should be looked for.
- Skin turgor, mucous membranes, and dependent edema are helpful in the classification of the etiology of hyponatremia.
- Focused examination to determine the status of CHF or cirrhosis yields information for management and prognosis.

Laboratory diagnosis

- Serum sodium should be corrected for elevated glucose, protein, or lipid.
- Urine sodium of <20 mEq/L suggests an intact renal concentrating mechanism.
- Urine urea levels are helpful when medications or IV fluids confound the value of urine sodium.
- Urine osmolality <100 mOsm/L (particularly with low urine sodium) suggests an intact renal concentrating mechanism, and predicts sodium correction with conservative measures.
- Urine osmolality >300 mOsm/L, or greater than the measured serum osmolality, suggests some major or minor component of SIADH.

Treatment

Treatment rationale

- Initial treatment depends on the suspected etiology for the hyponatremia. Initial labs and urine studies should be obtained prior to starting therapy.
- In all cases, stimuli for increased ADH secretion such as pain and nausea must be treated.
- Hypervolemic patients may require directed management of their underlying reasons for decreased effective intravascular volume.
- Patients who are hypovolemic must have their volume status restored with intravenous fluids. After initial stabilization, serum sodium should be reassessed, and a treatment plan started to increase the serum sodium by no more than 0.5 mEq/L/h or 12 mEq in 24 hours.
- Initial resuscitative efforts often mitigate several stimuli for increased ADH secretion all at once, resulting in a rapid increase in serum sodium.
- If at any point the rise in sodium is too rapid, isotonic infusions should be held, and rapid reduction of sodium with free water and desmopressin should be considered.
- The Adrogue–Madias equation can be used to calculate a dose of intravenous fluid to replace the serum sodium at an acceptable rate. If the medical history, the urine studies, and the trend in serum sodium suggest SIADH, isotonic infusions should be discontinued, and hypertonic saline should be considered if free water restriction fails to improve the serum sodium.

$$\text{Change in serum } \left(Na^{+}\right) = \frac{\text{infusate } \left(Na^{+}\right) - \text{serum } \left(Na^{+}\right)}{\text{total body water } + 1}$$

When to transfer to the ICU

- Most patients with hyponatremia can be managed on the general medical floor, provided that frequent blood samples can be obtained to monitor therapy.
- Patients potentially requiring hypertonic saline administration, or patients with neurologic findings, should be monitored in the ICU.
- Patients who exhibit seizures or symptoms of cerebral edema with a serum sodium <115 mEq/L require emergent administration of hypertonic saline.
- The calculation of a negative electrolyte free water clearance suggests that free water restriction and isotonic saline may not be adequate in correcting the hyponatremia.

Table of treatment

Treatment	Comments
Conservative treatment of pain and nausea: PO challenge	For patients with mild to moderate hyponatremia, with correctable or temporary causes
Free water restriction	Hypervolemic patients, psychogenic polydipsia
Salt tablets	Euvolemic patients with low solute intake, i.e. 'tea and toast diet'
Isotonic saline	Appropriate for most patients, dose calculated by the Adrogue–Madias equation
2% or 3% hypertonic saline	For patients with seizures, or patients with confirmed SIADH for whom isotonic saline would decrease the serum sodium. Infuse at 0.25–1.0 mL/kg/h
Desmopressin 0.3 μg/kg	Used along with free water to reverse overly rapid correction of serum sodium. Replaces ADH which had driven the hyponatremia and was lost in the initial treatment

Prevention/management of complications

- Rapid overcorrection of serum sodium can result in central pontine myelinolysis. This can be prevented by avoiding rates of sodium correction of >0.5 mEq/h.
- In the event of a significant overcorrection, the serum sodium must be rapidly decreased to the appropriate level for that point in time. This is accomplished by administering IV D5W. Given that this phenomenon is the result of suppression of ADH after the removal of its stimuli, exogenous ADH in the form of desmopressin may be required to reduce the sodium to previous levels.
- Once the sodium has returned to previous levels, conservative measures are generally adequate to increase the serum sodium appropriately.

Potential pitfalls/common errors

- The etiology for hyponatremia is often multifactorial, with SIADH being a major or minor component. Treatment of the reversible physiologic causes for ADH secretion must be taken into account.
- Volume resuscitation may correct the physiologic stimuli for increased ADH secretion. Sodium replacement during or after this can result in overly rapid correction of serum sodium as ADH secretion falls appropriately.

Prognosis

- Hyponatremia is a manifestation of a clinical condition causing increased ADH secretion and impaired water excretion.
- It is shown to portend a worse prognosis when seen in conditions such as congestive heart failure and cirrhosis.
- Hyponatremia presenting with seizures is life threatening.
- Complications in correction of hyponatremia (e.g. central pontine myelinolysis) can be severe.

CLINICAL PEARLS

- All forms of hyponatremia are due to increased ADH secretion, and some are due to SIADH. This distinction directs treatment and predicts complications.
- Reassess after initial fluid resuscitation. The physiology of ADH secretion changes.
- Low urine osmolality and sodium in the setting of hyponatremia is an appropriate corrective response and responds to conservative measures.
- High urine osmolality suggests a component of SIADH. All sources of free water should be limited in this setting.

Hypernatremia

BOTTOM LINE

- Hypernatremia may be due to the loss of electrolyte free water or the addition of excess sodium.
- Extracellular or serum sodium concentration depends on total body sodium and potassium concentration, in relation to total body water.
- Treatment involves estimating the free water deficit, and replacing it at a rate targeted at lowering the sodium by 0.5 mEq/h.

Background

Definition of disease

- Acute hypernatremia develops over less than 48 hours.
- Chronic hypernatremia develops and persists over 48 hours.

Incidence/prevalence

- The majority of patients affected by hypernatremia are older than 60 years of age.

Etiology

- Loss of electrolyte free water, which is not replaced due to impaired thirst mechanism or dependence on others for replacement.
- Ingestion of excess sodium.
- Diabetes insipidus.

Pathophysiology

- Water moves passively across all body compartments while concentrations of various electrolytes are maintained by active transport. This results in a higher concentration of sodium extracellularly, and a higher potassium concentration intracellularly.
- Serum sodium concentration depends on the total amount of sodium and potassium in total body water. Depletion of total body water from gastrointestinal, urinary, insensible, or oral losses, can transiently result in hypernatremia.

Predictive/risk factors

- Dependence on others for water (infants or, particularly, bedbound patients).
- Hypovolemia related to secretory diarrhea.
- Medications with a high sodium load.
- Medications that cause nephrogenic diabetes insipidus (e.g. lithium).
- Neurosurgery (central diabetes insipidus).

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Initial labs should include serum sodium and urine osmolality.
- A detailed history will almost always provide the etiology of the hypernatremia.

Typical presentation

- Patients with hypernatremia often present from a chronic care facility where they have been bedridden and have not had access to water unless it was provided to them. They may develop hypernatremia during the course of an inpatient illness where they receive intravenous medications with a high sodium load (e.g. hypertonic saline or, classically, piperacillin/tazobactam).
- Patients with nephrogenic or central diabetes insipidus typically present with a high urine output, often greater than 3 L per day. Nephrogenic causes may relate to medications, such as lithium. Central diabetes insipidus may be associated with a structural abnormality in the brain affecting the hypothalamus or posterior pituitary gland.

Clinical diagnosis

History

- The history and physical examination will usually yield a cause for the diagnosis. Chronicity of the hypernatremia must be determined.

Physical examination

- Neurologic signs and symptoms should be evaluated.
- Skin turgor, mucous membranes, and overall volume status should be determined.

Laboratory diagnosis

- Serum sodium and urine osmolality should be determined initially.
- Serial determinations of serum sodium are needed to monitor response to therapy.
- Urine osmolality above 600 is associated with extrarenal water losses. A urine osmolality <300 mOsm/L is associated with diabetes insipidus.

Treatment

Treatment rationale

- For patients with acute hypernatremia, occurring over less than 48 hours, the sodium should be corrected to 140 mEq/L over 24 hours. Idiogenic osmoles have not yet affected the tonicity of the brain, and edema is unlikely. Various regimens have been suggested – all employing calculation of the free water deficit. The entire free water deficit should be replaced over 24 hours.
- Chronic hypernatremia should be corrected more carefully with a goal correction rate of 0.5 mEq/L/h. Useful approximations to achieve this rate of change during the first 24 hours have been described. One method is to replace 30 mL/kg of free water in the first 24 hours. Another is to replace half of the calculated free water deficit in 24 hours.

$$\text{Water deficit} = \%\ \text{body water} \times \text{mass (kg)} \times \left(\frac{\text{current Na} - \text{ideal Na}}{\text{ideal Na}} \right)$$

- The rate of change should be monitored every few hours, and infusion rates should be adjusted as needed. Recalculation of the free water deficit at regular intervals may be helpful, particular when excretion of sodium and water can be variable.

When to admit to the ICU

- Most patients with hypernatremia can be managed on the general medical floor, provided that frequent blood samples can be obtained to monitor therapy.

Table of treatment

Treatment	Comments
Normal saline	To restore euvolemia. Reassessment of the free water deficit is necessary after volume repletion
5% Dextrose in water	Infusate which provides free water
5% Dextrose in 0.45% sodium chloride	Provides volume replacement and free water
Free water, by mouth	Results in a slower rate of correction of sodium level
Potassium	For repletion of ongoing losses; note that IV formulation will decrease the percentage of free water in solution

Prevention/management of complications

- Rapid overcorrection of serum sodium can result in cerebral edema. Monitoring sodium levels frequently during correction and making appropriate changes in the infusion rate can prevent this.

Potential pitfalls/common errors

- Initial volume resuscitation with isotonic solution may be required, or may have already been performed. In this situation, a repeat serum sodium level should be obtained soon after.
- Sodium and water loss during treatment is difficult to determine and alters the rate of reduction of serum sodium. For this reason, frequent monitoring of the serum sodium with appropriate adjustment of the infusion of free water is needed.

Prognosis

- Hypernatremia is generally easily correctable, although it requires close monitoring.
- Severe hypernatremia is associated with neurologic injury.
- Overly rapid correction of hypernatremia, if chronic, can result in cerebral edema.

CLINICAL PEARLS

- History is paramount in the determination of the etiology of hypernatremia.
- Calculate the free water deficit after initial resuscitation.
- In acute hypernatremia, replace the entire free water deficit in 24 hours with D5W or by mouth.
- In chronic hypernatremia, lower the serum sodium level by 0.5 mEq/L/h, not to exceed 8–10 mEq in the first day.

Hypercalcemia

BOTTOM LINE

- Hypercalcemia is most often due to malignancy or hyperparathyroidism.
- Ionized calcium is the physiologically active form.
- Treatment depends on the corrected serum calcium levels, clinical symptoms, and underlying etiology.

Background

Definition of disease

- Hypercalcemia is elevation of the ionized, physiologically active form of calcium.

Incidence/prevalence

- Hypercalcemia is often found incidentally, as it is frequently asymptomatic, so the precise epidemiology is unknown.

Etiology

- Hypercalcemia is either mediated by PTH or is independent of it.
- PTH-mediated hypercalcemia is primary or familial hypercalcemia.
- PTH-independent causes of hypercalcemia include malignancy, sarcoidosis, and vitamin D excess.

Pathophysiology

- Calcium metabolism is normally regulated by PTH. Increased serum calcium may therefore be due to increased PTH.
- PTH is increased in primary and familial hyperparathyroidism, and is associated with low levels of phosphate. Alternatively, hypercalcemia may be independent of PTH secretion, and therefore markedly unregulated.
- Some cancers (particularly squamous cell carcinoma) secrete PTH-related protein, which is a normal protein that is secreted in excess, and can stimulate the PTH receptor. Lytic metastases to bone also release calcium into the serum.
- Some malignancies as well as sarcoidosis are associated with increased calcitriol resulting in increased intestinal absorption of calcium.

Predictive/risk factors

- Familial or primary hyperparathyroidism.
- Cancers, particularly squamous cell, and lymphomas.
- Granulomatous diseases, including sarcoidosis.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Elevated calcium levels should be confirmed by repeating the relevant test, and obtaining an ionized calcium level.
- A careful history for associated diseases, symptoms, and chronicity should be obtained.
- Serum albumin should be measured, as inactive calcium is bound to albumin.
- The serum PTH level must be determined, as PTH-mediated versus PTH-independent causes must be differentiated.
- Calcidiol and calcitriol levels should be obtained to evaluate for etiologies such as excess vitamin D ingestion, lymphoma, or sarcoidosis.
- In the setting of malignancy and low levels of PTH, PTH-related peptide (PTHrP) and the analog of PTH secreted by some malignancies, should be measured. Urinary calcium levels may be helpful.

Typical presentation

- Many patients are asymptomatic, and hypercalcemia is noted incidentally.
- Patients with mild elevations in calcium may have non-specific symptoms of fatigue or abdominal discomfort.
- More severe elevations in calcium are associated with dehydration, nausea, objective muscle weakness, nephrolithiasis, renal tubular acidosis, cardiac arrhythmia, bone pain, and neurologic disturbances.

Clinical diagnosis

History

- The level of ionized calcium should be determined, along with other labs as indicated, as well as a history of comorbid conditions and chronicity.

Physical examination

- Neurologic abnormalities, objective muscular weakness, evidence of malignancy, and signs of volume depletion can be seen in hypercalcemia.

Laboratory diagnosis

- Serum calcium and albumin should be obtained first, and the corrected calcium level should be determined.
- Ionized calcium levels can be obtained.
- Vitamin D, PTH, and PTHrP levels may be indicated.

Treatment

Treatment rationale

- Treatment depends on the level of calcium. Patients with a calcium level <12 mg/dL require avoidance of medications associated with hypercalcemia, and adequate hydration.
- Calcium levels between 12 and 14 mg/dL require volume repletion as well as initiation of a bisphosphonate.
- Severe hypercalcemia, with levels >14 mg/dL, require aggressive sodium chloride infusion titrated to a urine output of >150 mL/h. Calcitonin and zolendronic acid may be administered.
- Calcium should be corrected for the patient's serum albumin:
  - Corrected calcium = [0.8 × (4 – patient's albumin (g/dL))] + Serum calcium (mg/dL).

When to admit to the ICU

- Patients with mild hypercalcemia in the setting of sarcoidosis or another known cause can be followed in the outpatient setting.
- Severe hypercalcemia requires inpatient evaluation and management. Hypercalcemia requires treatment in an ICU generally when other complicating factors contribute to critical illness.

Table of treatment

Treatment	Comments
Conservative: oral hydration, avoidance of medications associated with hypercalcemia	For patients with corrected calcium levels <12 mg/dL
Normal saline	For patients with corrected calcium levels >12 mg/dL
Pamidronate	Can be used in patients with corrected calcium levels >12 mg/dL. Onset of action is 2–4 days Dosing: 30 mg daily, administered as a 4 hour infusion on three consecutive days for a total dose of 90 mg
Calcitonin	For patients with corrected calcium levels >14 mg/dL. Onset of action is 12–24 hours Dosing: start at 4 IU/kg every 12 hours; can increase to as much as 8 IU/kg every 6 hours
Zolendronic acid	For patients with corrected calcium levels >14 mg/dL, and in the setting of malignancy Dosing: 4 mg infused over no less than 15 minutes every 3–4 weeks
Hemodialysis	For patients in renal failure, or when serum calcium levels are >18 mg/dL

Prevention/management of complications

- Adequate hydration and urine output are essential for the prevention of nephrolithiasis.

Potential pitfalls/common errors

- A single lab finding of an elevated calcium should be repeated for confirmation.
- Calcium should be corrected for the patient's serum albumin:
  - Corrected calcium = [0.8 × (4 – patient's albumin (g/dL))] + Serum calcium (mg/dL).

Prognosis

- Severe hypercalcemia is associated with comatose states, cardiac arrhythmia, and renal failure, and is often seen in the setting of significant underlying comorbidity.

> **CLINICAL PEARLS**
> - Hypercalcemia may be mediated by primary/familial hyperparathyroidism, or may be independent of PTH.
> - PTH-independent causes of hypercalcemia tend to be associated with significant comorbidities, and with higher serum concentrations of calcium.
> - Treatment includes volume repletion, and may require pharmacologic agents.

Hypocalcemia

> **BOTTOM LINE**
> - Hypocalcemia is typically a manifestation of another underlying condition.
> - Hypocalcemia leads to neuromuscular irritability and tetany, fatigue, paresthesias, and seizures.

Background

Definition of disease

- Hypocalcemia is generally regarded as an ionized calcium level <1.0 mmol/L or a serum calcium level of <8.5 mg/dL when corrected for albumin.

Etiology

- Hypoparathyroidism, or partial or surgically absent parathyroid glands.
- Vitamin D deficiency.
- Chronic renal disease, and hyperphosphatemia.
- Saponification, which can be seen in severe pancreatitis.
- Chelation with citrate, which is used in packed red blood cell transfusions.

Pathophysiology

- PTH is secreted in response to low levels of calcium. PTH increases serum calcium by absorbing calcium from the renal tubule, the bones, and by increasing production of calcitriol, which in turn reabsorbs calcium from the intestine.
- A decrease in the activity of PTH results in hypocalcemia and hyperphosphatemia.
- Decreased parathyroid activity can be seen in cases of autoimmune hypoparathyroidism, or after surgical removal of parathyroid glands. Alternatively, low serum calcium may be associated with a physiologically elevated PTH level, as in the case of vitamin D deficiency or renal disease.
- In renal disease, serum phosphate rises due to impaired excretion. Hyperphosphatemia stimulates the release of PTH, and subsequently results in hypocalcemia.
- Acute pancreatitis can result in saponification in the abdominal cavity, which will decrease serum calcium levels.

Predictive/risk factors

- Chronic renal disease.
- Vitamin D deficiency.

Prevention

- Routine lab work for at-risk patients is adequate for surveillance.
- Patients receiving several units of packed red blood cells may need calcium repletion.
- Patients with acute pancreatitis and decreasing calcium levels may need closer monitoring.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Initial labs should include a serum calcium and albumin, and a corrected calcium concentration should be determined.
- A detailed history including that of thyroid surgery and renal disease should be obtained.
- The PTH level will classify the etiology of the hypocalcemia.

Typical presentation

- Patients often present with non-specific symptoms.
- More severe hypocalcemia can present with tetany, seizures, and altered mentation.
- Arrhythmias may also occur.

Clinical diagnosis

History

- Severe hypocalcemia is often associated with a significant predisposing factor, such as thyroid surgery or pancreatitis.

Physical examination

- Tetany, carpopedal spasm, Chvostek sign (facial nerve hypercontractility to finger tap) and Trousseau sign (wrist and hand contraction in response to 3 minutes of blood pressure cuff inflation) may be seen.

Laboratory diagnosis

- Ionized calcium levels, or serum calcium levels corrected for albumin, should be obtained.
- Other electrolytes should be measured as hypomagnesemia can alter calcium metabolism.
- PTH levels are normal or low in the setting of PTH-mediated hypocalcemia.
- PTH levels are elevated in the setting of hypocalcemia due to chronic renal disease, and vitamin D deficiency.

Treatment

Treatment rationale

- Like other electrolyte derangements, hypomagnesemia must be corrected before calcium will correct.
- IV calcium is indicated for hypocalcemia, with neuromuscular irritability, seizures, and arrhythmias.
- Calcium chloride (500–1000 mg IV over 5–10 minutes; repeat as necessary) contains three times the elemental calcium that is in the same volume of calcium gluconate (0.5–2.0 mg/kg/h IV; not to exceed 4 g over 4 hours.

- Some patients with severe hypocalcemia and significant neurologic symptoms require repeated infusions and serial monitoring of calcium levels, followed by daily oral supplementation.

When to admit to the ICU

- Symptomatic or moderate to severe hypocalcemia will require admission and monitoring.
- Tetany requires ICU admission and telemetry.

Table of treatment

Treatment	Comments
Calcium gluconate	For intravenous calcium repletion
Calcium chloride	Provides a higher amount of intravenous calcium repletion
Calcium citrate	Used chronically for at-risk patients
Vitamin D	Used concurrently with oral supplementation

Prevention/management of complications

- Close monitoring of calcium levels with attention to related factors, including vitamin D and magnesium, is required as calcium metabolism is complex and dependent on several factors.

Potential pitfalls/common errors

- Like other electrolyte derangements, hypomagnesemia must be corrected before calcium will correct.

Prognosis

- Depending on the etiology, hypocalcemia may be acutely correctable, require chronic management, or be a sign of severe, life-threatening organ dysfunction.

CLINICAL PEARLS

- Severe hypocalcemia presents with neuromuscular irritability and cardiac arrhythmia, and may require several doses of intravenous calcium.
- Calcium chloride provides a significantly higher amount of elemental calcium than calcium gluconate.
- Persistent hypocalcemia should raise the concern of calcium deposition or saponification.

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Guidelines

National society guidelines

Title	Source	Date and reference
Hypokalemia		
New Guidelines for Potassium Replacement in Clinical Practice: A Contemporary Review by the National Council on Potassium in Clinical Practice	National Council on Potassium in Clinical Practice	2000 Arch Intern Med 2000;160(16):2429–36
Hyperphosphatemia		
KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)	Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group	2009 Kidney Int 2009;Suppl 113:S1–130
Hyponatremia		
Clinical Practice Guideline on Diagnosis and Treatment of Hyponatraemia	Hyponatraemia Guideline Development Group	2014 Nephrol Dial Transplant 2014;29(Suppl 2):i1–39
Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations	Expert Panel findings	2007 Am J Med 2007;120:S1

International society guidelines

Title	Source and comment	Date and reference
Hyperkalemia		
European Resuscitation Council Guidelines for Resuscitation 2005 Section 7. Cardiac Arrest in Special Circumstances	European Resuscitation Council Synopsis of management of life threatening electrolyte disorders	2005 Resuscitation 2005;67(Suppl 1):S135–70

Evidence

Type of evidence	Title and comment	Date and reference
Hyperkalemia		
Prospective cohort study	*Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients* Described odds ratio for development of hyperkalemia in patients on chronic hemodialysis who take ACEI or ARB	2002 Am J Med 2002;112(2):110–14
Case–control study	*Beta-blockers, trimethoprim-sulfamethoxazole, and the risk of hyperkalemia requiring hospitalization in the elderly: a nested case-control study* Showed the association between using TMP-SMX and development of hyperkalemia in the elderly.	2010 Clin J Am Soc Nephrol 2010;5(9):1544–51
Hypokalemia		
Multicenter survey	*Older age and in-hospital development of hypokalemia from loop diuretics: results from a multicenter survey. GIFA Investigators. Multicenter Italian Pharmacoepidemiologic Study Group* Proved a relationship between older age and development of in-hospital hypokalemia. Also showed a similar but independent relationship with those taking loop diuretics	2000 J Gerontol A Biol Sci Med Sci 2000;55(4):M232–8
Hypophosphatemia		
Prospective cohort	*Hypophosphatemia in critically ill children: prevalence and associated risk factors* Identified association between dopamine, malnutrition, respiratory disease, and the development of hypophosphatemia	2009 Pediatr Crit Care Med 2009;10(2):234–8
Retrospective case–control	*Predictors of hypophosphatemia during refeeding of patients with severe anorexia nervosa* Identified risk factors for refeeding among patients with anorexia nervosa	2015 Int J Eat Disord 2015;48(7):898–904
Retrospective, observational study	*A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support* *Proposed an algorithm for phosphorus replacement in critically ill trauma patients*	2006 J Parenter Enteral Nutr 2006;30(3):209–14

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

with website

CHAPTER 53

Acid–Base Disorders

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OVERALL BOTTOM LINE

- Acid–base balance is tightly regulated in the body and mediated through interactions of CO_2 and H^+ ions. Buffering proteins and physiologic changes in both the lung and kidney are key to this acid–base balance.
- Internal validity of a blood gas must be established prior to interpretation and subsequent clinical decision making.
- A systematic approach is required to identify one or multiple concurrent acid–base disorders.
- Appropriate compensation of an acid–base anomaly must be assessed, and, if absent, an additional disorder should be identified.
- Identifying acid–base abnormalities in the proper clinical setting may lead to clinical treatment changes.

Background

- The pH of plasma is tightly controlled at a pH of 7.40. The interaction of and effect of changes in CO_2 and HCO_3 on pH are defined by the Henderson–Hasselbalch equation:

$$pH = 6.1 + \log\left(\left[HCO_3^-\right] / \left(PCO_2 \times 0.3\right)\right)$$

- Normal pH is maintained by three mechanisms:
  - Regulation of PCO_2: normal PCO_2 is 40 mmHg and is regulated by changes in alveolar ventilation:
    - PCO_2 = VCO_2 (CO_2 production) × 0.863/alveolar ventilation.
  - Regulation in H^+ ion concentration: renal excretion of H^+ and reabsorption of HCO_3^- regulates the normal HCO_3^- concentration at 24 mEq/L.
  - Intrinsic buffering: mediated by serum phosphates and serum anionic proteins.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Etiology

Acid–base disorder	Etiology	
Respiratory acidosis	Decreased minute ventilation: • ↑ Airway resistance (asthma, COPD, upper airway obstruction) • ↓ Central respiratory drive (CNS injury, sedating drugs) • ↑ Dead space and V/Q mismatch (severe pulmonary embolism, parenchymal disease) • Neuromuscular weakness (neuromuscular disease, tiredness due to prolonged and increased work of breathing) ↑ CO_2 production (fever, shivering, ↑ carbohydrate diet, hyperthyroidism)	
Respiratory alkalosis	Acute	Pain, anxiety Hypoxia CNS stimulants Fever and sepsis ↑ Excessive ventilation on mechanical ventilator, post-intubation
	Chronic	Pregnancy Liver disease
Metabolic acidosis	↑ Anion gap	MUDPILES (see later)
	Normal anion gap	GI HCO_3^- loss: diarrhea Renal HCO_3^- loss: type 1–4 renal tubular acidosis
Metabolic alkalosis	HCO_3^- gain (milk alkali syndrome, HCO_3^--rich fluids) H^+ loss from GI (vomiting) or dehydration ➔ contraction alkalosis Excessive renal loss of chloride (diuretics) Post-hypercapnia	

Diagnosis

Five-step approach

Systematically and accurately identifying one or multiple acid–base disturbances is vital to initiate or change management. Once the primary and secondary disturbances are identified, appropriate testing and treatment may be initiated.

Step 1: assess internal validity

- Identifying acid–base disturbances can only be done if a blood gas is internally valid, thereby allowing its accurate interpretation. An ABG and serum chemistry taken simultaneously are assessed by the following two step approach:
  - Know the pH.
  - Calculate the expected H^+ concentration.
- There is a linear relationship between the expected $[H^+]$ ion concentration and pH between 7.25 and 7.5. Within that range, for every change in $[H^+]$ in one direction there is an expected change in pH of 0.01 in the opposite direction.
- At pH below 7.25 there is a slightly greater change in $[H^+]$ for a given drop in pH; conversely at pH above 7.5 there is slightly less of a change in $[H^+]$ for a given change in pH (Table 53.1).
- Next, calculate the measured H^+ concentration on the blood gas using the modified Henderson–Hasselbalch equation:

$$\left[H^+\right] = 24 \times \left(PaCO_2 / \left[HCO_3^-\right]\right)$$

Table 53.1 Relationship between pH and [H⁺] ion concentration.

pH	$[H^+]$ (mmol/L)	pH	$[H^+]$ (mmol/L)
7.00	100	7.35	45
7.05	89	7.40	40
7.10	79	7.45	35
7.15	71	7.50	32
7.20	63	7.55	28
7.25	56	7.60	25
7.30	50	7.65	22

- The expected and calculated H^+ concentration should be similar. If discordant, the blood gas is not internally consistent and therefore should not be used for interpretation of acid–base abnormalities. The reasons for invalidity may be related to sample collection (venous versus arterial sample, samples not on ice, entrained ambient air into the sample, extremes of temperature).
- An additional way to assess validity is to compare the serum HCO_3^- (which is directly measured) and the HCO_3^- on the blood gas (which is calculated automatically using the Henderson–Hasselbalch equation). If a blood gas is internally valid, the measured and calculated $[HCO_3^-]$ should be similar.

Step 2: assess the primary acid–base disorder

- Acidemia refers to a serum pH <7.40. Alkalemia refers to a serum pH >7.40. This is further classified by cause:
  - Respiratory acidosis: ↓ pH, ↑ PCO_2.
  - Respiratory alkalosis: ↑ pH, ↓ PCO_2.
  - Metabolic acidosis: ↓ pH, ↓ PCO_2.
  - Metabolic alkalosis: ↑ pH, ↑ PCO_2.
- Note that there may be one or more acid–base abnormalities even when pH is at or near normal (7.35–7.45). This is due to the tight interaction and regulation of $PaCO_2$ and HCO_3^-. Therefore look beyond the pH to assess for abnormalities in $PaCO_2$ and HCO_3^-.

Step 3: assess for appropriate compensation

- Changes in $PaCO_2$ are offset by changes in HCO_3^- in the opposite direction (and vice versa) in an attempt to normalize the pH; however, most compensation is not complete and does not fully correct pH to normal.
- When assessing compensation, if a response is not appropriate, then an additional acid–base disorder is present. Table 53.2 details the expected compensation for the given primary disturbance.

Table 53.2 Expected compensation for acid–base disorders.

Primary disorder	HCO_3^- and $PaCO_2$	Expected compensation	
Metabolic acidosis	↓pH ↓PCO_2	Winter's formula: $PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$	
Metabolic alkalosis	↑pH ↑PCO_2	$\Delta PCO_2 = 0.6 \times HCO_3^- \pm 2$	
Respiratory acidosis	↓pH ↑PCO_2	Acute	↑PCO_2 by 10, ↑HCO_3^- by 1, ↓pH by 0.008
		Chronic	↑PCO_2 by 10, ↑HCO_3^- by 4–5, ↓pH by 0.003
Respiratory alkalosis	↑pH ↓PCO_2	Acute	↓PCO_2 by 10, ↓HCO_3^- by 2, ↑pH by 0.008
		Chronic	↓PCO_2 by 10, ↓HCO_3^- by 3.5-4, ↑pH by 0.003

Step 4: calculate the anion and osmolal gaps

- The anion gap (AG) is calculated as:

$$AG = Na - \left(Cl^- + HCO_3^-\right)$$

- The normal AG is 12 mEq/L.
- Since albumin is the major unmeasured anion, the expected 'normal anion gap' should be corrected for patients with hypoalbuminemia. For every drop in albumin of 1 g (below 4 g/dL) the AG decreases by 2.5 mEq/L. For example, a patient with an albumin of 2 g/dL would have an expected AG of 7 mEq/L.
- The differential diagnosis for an elevated AG is described with the mnemonic MUDPILES:
  - *M*ethanol, *M*etformin.
  - *U*remia.
  - *D*iabetic/starvation/alcoholic ketoacidosis.
  - *P*araldehyde.
  - *I*soniazid.
  - *L*actic acidosis (shock, metformin, methemoglobinemia, CO, cyanide, type B lactate).
  - *E*thylene glycol.
  - *S*alicylates.
- When an AG is present, an osmolal gap should be calculated, since many anions that contribute to an AG will contribute to an osmolal gap as well. This is done by comparing the difference between the measured and expected serum osmolarities:
  - Osmolal gap = measured osm – (2 × Na + BUN/2.8 + glucose/18 + ethanol/4.6).
  - A normal osmolal gap is <10.
  - The osmolar gap is increased in the presence of ethanol, ethylene glycol, methanol, acetone, isopropyl ethanol, and propylene glycol.

Step 5: assess the delta ratio or the delta-delta gap

- Under normal circumstances, the total body cations and anions are matched to maintain electrical neutrality. Any increase of an unmeasured anion will therefore increase the AG. It is expected that a change in unmeasured anions (which contribute to the AG) is matched by a change in [HCO_3^-].
- The delta ratio (Δ/Δ) is calculated as:
  - Delta ratio = $\Delta AG/\Delta HCO_3$ = (calculated AG – normal AG)/(normal HCO_3^- – measured HCO_3^-).
  - Delta ratio = (AG – 12)/(24 – HCO_3^-).
- If the delta ratio is 1–2, a pure AG metabolic acidosis is present.
- If the delta ratio is <1, a larger than expected drop in HCO_3^- has occurred due to a concomitant non-AG metabolic acidosis.
- If the delta ratio is >2, a smaller drop in HCO_3^- has occurred due to a concomitant metabolic alkalosis.
- Alternatively, the delta-delta gap (Δ-Δ) can be calculated:

  Delta-delta gap = ΔAG (delta anion gap) – ΔHCO_3 (delta bicarbonate gap)
  = (calculated AG – normal AG) – (normal HCO_3^- – measured HCO_3^-)
  = (Na – (Cl^- + HCO_3^-) – 12) – (24 – HCO_3^-) = Na – Cl^- – 36
- If the Δ-Δ gap is between –6 and 6, a pure AG metabolic acidosis is present.
- If the Δ-Δ gap is <–6, a larger than expected drop in HCO_3^- has occurred due to a concomitant non-AG metabolic acidosis.
- If the Δ-Δ gap is >6, a smaller drop in HCO_3^- has occurred due to a concomitant metabolic alkalosis.

Clinical presentations and further diagnostic steps for acid–base disorders

Acid–base disorder	Clinical presentation	Further diagnostic steps
Respiratory acidosis	Acute: increasing stupor, skin flushing, myoclonus and/or asterixis Chronic: attenuated symptoms or asymptomatic	None
Respiratory alkalosis	Lightheadedness and possible syncope due to rise in CSF pH and cerebral vasoconstriction. Can have seizures, arrhythmias, and symptoms of hypocalcemia (acute ↓ ionized Ca^{2+})	None
Metabolic acidosis	Kussmaul respirations for respiratory compensation (increased tidal volume relative to respiratory rate). Coma, hypotension, bradycardia, and cardiac arrest in severe cases	Normal AG then calculate urine AG: Urine (Na^+ + K) – Cl^- If urine AG is negative (normal) then this suggests GI source; if urine AG is positive then this suggests renal tubular acidosis
Metabolic alkalosis	Non-specific: weakness, myalgia, polyuria, cardiac arrhythmias and hypoventilation	Measure urine Cl^-; if <20 then likely chloride-responsive metabolic alkalosis

Treatment

Treatment rationale

Treatment should be aimed at the underlying disorder that has caused the acid–base disorder. Table 53.3 delineates specific treatment modalities that are dependent on the individual patient's presentation.

When to admit to the ICU

- Life-threatening acid–base abnormality such as severe acidemia or alkalemia.
- Uncompensated acute respiratory acidosis.
- Acidosis due to lactic acid or toxic alcohol ingestion.

CLINICAL PEARLS

- A pH at or near 7.40 does not exclude acid–base abnormalities; assess the anion gap, CO_2, and HCO_3^- closely and systematically to identify multiple possible anomalies.
- In all cases of possible unintentional or intentional toxic ingestion, an osmolal gap should be calculated. Early ingestion of toxic alcohols may manifest as only an osmolal gap before the alcohol is metabolized to produce lactic acid, prompting early definitive treatment.
- In cases of metabolic alkalosis, it is essential to identify patients who are chloride responsive and to ensure adequate K^+ repletion.

Prognosis

Follow-up tests and monitoring

- Once one or multiple acid–base abnormalities are identified, appropriate treatment directed toward correction of these anomalies must be monitored closely. Repeat blood gases and serum chemistries must be frequently checked, especially in the early stages of treatment.
- Examples include: repeat chemistry to ensure closure of anion gap; repeat arterial blood gas to ensure resolution of acute respiratory acidosis after initiation of non-invasive ventilation; and serial blood gases and chemistries to assess for contraction alkalosis while using diuretics.

Table 53.3 Treatments for acid–base disorders.

Acid-base disorder	Treatment
Respiratory acidosis	Aimed at correcting underlying disorder Examples: • Reverse sedating meds • Bronchodilators and/or steroids for airway obstruction • Assist ventilation with non-invasive positive pressure ventilation or mechanical ventilation depending on the patient's clinical picture Avoid $NaHCO_3$ administration: HCO_3^- combines with H^+ to generate H_2O and ↑$PaCO_2$
Respiratory alkalosis	Aimed at correcting underlying disorder Examples: • Treat pain and anxiety with opioids and benzodiazepines • Treat hypoxia or sepsis
Metabolic acidosis	Aimed at correcting underlying disorder Examples: AG: • Diabetic ketoacidosis – give insulin and intravenous fluid • Lactic acidosis – treat sepsis, volume resuscitation, etc. • Toxic alcohols – hemodialysis, fomepizole • Removal of meds (e.g. lorazepam containing polyethylene glycol, isoniazid) Non-AG: • Correction of diarrhea or renal insult • HCO_3^- supplementation in a form of sodium bicarbonate; can use oral or intravenous route based on urgency and the patient's volume status.
Metabolic alkalosis	Aimed at correcting underlying disorder Examples: • Control of vomiting, limiting diuretic use, eliminating extrinsic HCO_3^- administration • Cl^- responsive metabolic alkalosis (volume contraction) treated with saline to achieve euvolemia • Replete chloride (KCl preferred) • Acetazolamide may be used if alkalosis persists despite euvolemia with saline and KCl supplementation

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Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

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PART 8

Hematology and Oncology

Section Editor: Hooman Poor

CHAPTER 54

Blood Products and Transfusions

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OVERALL BOTTOM LINE

- The need for transfusion of blood products is common in critically ill patients.
- Packed red blood cells (PRBCs) are the most commonly transfused blood products with approximately 17 million RBC products transfused yearly in the USA.
- Other blood products, including plasma, prothrombin complex concentrates, platelets, and cryoprecipitate, are frequently used.

Blood products

Red blood cell preparations

- The majority of RBC products are PRBCs produced from donated whole blood in an anticoagulant preservative solution; 11% are collected by RBC apheresis.
- One unit typically contains 130–240 mL of RBCs, a total of 50–80 g of hemoglobin (Hb), and has a hematocrit (Hct) of 55–80%, with variation dependent upon the anticoagulant preservative solution used.
- Higher volume and lower Hct are found in additive solution-containing products.
- Unmodified RBC preparations contain small amounts of plasma, platelets, and leukocytes.
- In non-bleeding patients each RBC unit will increase the Hb by 1 g/dL and the Hct by 3%.
- Special preparations:
  - Leukocyte-reduced concentrates (<5 × 10^6 leukocytes in the final component in the USA): for use with repeated febrile non-hemolytic transfusion reactions, prevention of sensitization to HLAs for organ transplant patients, cytomegalovirus (CMV) and Epstein–Barr virus (EBV) transmission, and transfusion-related immunomodulation.
  - Washed PRBCs: removes plasma proteins, some leukocytes, and remaining platelets. Used for recurrent severe allergic transfusion reactions not prevented by antihistamines and IgA-deficient patients with anti-IgA antibodies.
  - Irradiated PRBCs: inactivate immunocompetent lymphocytes for prevention of transfusion-associated graft-versus-host disease (GVHD) in immunocompromised patients.
  - Frozen RBCs: long-term storage of rare RBC phenotypes for use in patients with related alloantibodies.
  - Volume-reduced RBCs: removal of plasma and supernatant for patients who are volume sensitive, have sensitivities to additive solution, and/or an increased potassium load.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Indications for PRBC transfusion

- Hemorrhagic shock.
- Acute hemorrhage and hemodynamic instability or inadequate oxygen delivery.
- Symptomatic anemia.
- Replacement of RBCs during exchange transfusion.
- Stable anemia in critically ill patients: restrictive strategy is recommended; trigger of Hb <7 g/dL in most patients and ≤8 g/dL in patients with acute coronary syndrome.

Plasma products

- Fresh frozen plasma (FFP): acellular fluid portion of blood which can be manufactured from whole blood or collected directly by apheresis.
  - Contains approximately 0.7–1 IU/mL of each clotting factor and 1–2 mg/mL of fibrinogen.
- Frozen plasma (FP24): plasma frozen at −18°C or colder within 24 hours after phlebotomy.
  - Considered to be clinically equivalent to FFP.
- Thawed plasma.
  - FFP or FP24 that has been thawed and stored for >24 hours.
  - Most clotting factors remain stable during the 5 days of storage. The activity of factors V, VII, and VIII declines significantly; however declines are not considered to be of clinical significance.
- Cryoprecipitate-reduced plasma: supernatant expressed during manufacture of cryoprecipitate from FFP.
  - Deficient in factors VIII, XIII, vWF, fibrinogen, cryoglobulin, and fibronectin.
  - Only used for transfusion or plasma exchange therapy in patients with thrombotic thrombocytopenic purpura.
- The majority of plasma units have a volume of about 250 mL.
- Estimated dosage is 10–15 mL/kg, which will increase factor activities by at least 30% in the absence of rapid ongoing consumption.
- Should be given as close to the time needed for surgery or procedure to maximize hemostatic effect.

Indications for FFP transfusion

- Multiple acquired coagulation factor deficiency.
- Replacement of single plasma factor deficiency for which no factor concentrate exists.
- Liver failure.
- Disseminated intravascular coagulation (DIC).
- Rapid reversal of warfarin.
- Plasma infusion or exchange for thrombotic thrombocytopenic purpura, thrombotic microangiopathies, diffuse alveolar hemorrhage, and catastrophic antiphospholipid syndrome.

Cryoprecipitate

- Cryoprecipitate is made from human plasma by refreezing the remains after the supernatant is removed from thawed FFP.
- Main constituents are fibrinogen, fibronectin, factor VIII, vWF, and factor XIII.
- One unit will increase fibrinogen concentration by approximately 50 mg/dL per 10 kg of body weight. Typical dose is 10 units.

Indications for cryoprecipitate transfusion

- Acquired/congenital hypofibrinogenemia.
  - Recommended for fibrinogen <100 mg/dL in actively bleeding patients or prior to surgery.
- Reversal of thrombolytic therapy with bleeding.
- Factor deficiencies if factor concentrates are not available.

Platelet products

- Can be manufactured from whole blood which usually requires pooling of multiple units (4–6 units) or from apheresis where one collection can usually provide multiple doses. Typical dose is 3–4 × 10^{11} platelets for an adult.
- Special preparations:
  - Leukoreduced: decreases febrile transfusion reactions, risk of CMV transmission, and HLA alloimmunization and resultant risk for platelet refractoriness.
  - Irradiated: prevents transfusion-associated GVHD.
  - Washed or volume reduced: removes antibodies contained within the plasma. Can lead to reduction of number of available platelets by 5–30% as well as decrease in platelet function.

Indications for platelet transfusion

- Therapeutic transfusion:
  - Actively bleeding patients with platelet count <50 000/μL or dysfunctional platelets.
- Prophylactic transfusion triggers:
  - For most patients <10 000/μL without active bleeding.
  - Consider <20 000/μL for bleeding, febrile, or septic patients.
  - Consider <50 000/μL for planned lumbar puncture, indwelling catheter insertion, or most invasive procedures.
  - Consider <100 000/μL for major surgery or procedures involving the eye or brain.
- Platelet dysfunction:
  - If underlying cause of platelet dysfunction cannot be corrected, if there is no improvement with RBC transfusion to Hct >30%, and if the use of desmospressin is inappropriate or does not prove effective.

Treatment protocols

Blood products for transfusion

- Obtain informed consent in non-emergent situations.
- Order appropriate blood product(s).
- Inform nursing staff.
- Obtain vascular access.
- Confirm patient identity and receipt of appropriate blood products.
- Monitor patient for complications during and after transfusion.
- Check follow-up labs.

Massive transfusion protocol (MTP)

- Typically defined as transfusion of 10 or more RBC products within 24 hours, but also defined as replacement of 50% of total blood volume within 3 hours, or blood loss exceeding 150 mL/min.
- As PRBCs and crystalloid volume expanders are infused, concentrations of platelets and clotting factors will decline.
  - Depletion of approximately 35% of coagulation factors after replacement of one blood volume.
  - Platelet concentration will decrease to approximately 50 000/μL and fibrinogen to approximately 100 g/dL after two blood volumes.
- Optimal ratios of blood products are unknown, however it is important to provide plasma and platelet products along with RBC products.
  - Better outcomes have been shown with equal ratio 1:1:1 dosing of PRBCs, plasma, and platelets.

- MTP can be managed by component therapy-based approaches, with transfusion triggers such as Hb <8 g/dL, PT >1.5 times normal, platelets <50 000/μL, and fibrinogen <100 g/dL.
- Frequent monitoring of platelets, PT, aPTT, and fibrinogen should be performed.
- Potential complications of MTP:
  - Coagulopathy.
  - Hypothermia.
  - Hyperkalemia.
  - Hypocalcemia.
  - Acid–base disorders.
  - Acute respiratory distress syndrome.

Adverse transfusion reactions

Potentially severe acute reactions

Allergic, urticarial, or anaphylactic reactions

- Onset: 0–4 hours; anaphylaxis onset is seconds to 45 minutes.
- Presentation: depending on severity, can have urticarial rash, generalized pruritis, erythema, angioedema, hoarseness, stridor, wheezing, hypotension, tachycardia, and even cardiac arrest.
- Incidence:
  - Platelets: 0.3–6%.
  - RBCs: 0.03–0.61%.
  - Plasma: 1–3%.
  - The majority of reactions are mild; anaphylaxis occurs in 1:20 000 components transfused.
- Prevention:
  - Leukoreduction is not beneficial.
  - Premedication is probably not beneficial, but may reduce symptoms in patients at high risk for reactions (prior history of reaction).
  - Plasma reduction of platelets may be beneficial.
  - Slower transfusion rates may help.
  - IgA deficient products for patients with IgA deficiency and anti-IgA antibodies.
- Treatment of severe reactions:
  - Discontinue transfusion.
  - Epinephrine 0.01 mg/kg with maximum of 0.5 mg intramuscularly to the thigh every 5 minutes.
  - Additional vasopressors as needed.
  - Intubation and mechanical ventilation if necessary.
  - Antihistamines.
  - Glucocorticoids.
  - H_2 antagonists.
- Treatment of mild reactions:
  - Temporarily stop transfusion.
  - Diphenhydramine or other antihistamine.
  - If symptoms resolve quickly can restart transfusion, otherwise discontinue.

Acute hemolytic reactions

- Onset: 0–24 hours after transfusion.
- Presentation: signs and symptoms include fever, chills, rigors, back and flank pain, hypotension, epistaxis, hemoglobinuria, oliguria or anuria, renal failure, DIC.

- Incidence:
  - True incidence is unknown.
  - In 2008 it was estimated to be 1:38 000 to 1:100 000 transfusions.
  - Risk of death is 1:1 500 000 transfusions.
- Prevention:
  - Strict adherence to pre-transfusion patient identification.
  - Administration of ABO-compatible blood products.
- Treatment:
  - Discontinue transfusion.
  - Fluid support with 10–20 mL/kg of isotonic fluids.
  - Diuretic to maintain urine output between 30 and 100 mL/h or more.
  - Vasopressor support as needed.
  - Transfusions of plasma, platelets, and/or cryoprecipitate as needed for bleeding and DIC.
  - Immediately notify transfusion service:
    - Clerical check of patient and blood product.
    - Return blood product for testing.

Sepsis

- Onset: 0–6 hours after transfusion.
- Presentation: symptomatic to fevers, rigors, hypotension, tachycardia, dyspnea.
- Incidence:
  - RBCs: approximately 1:30 000 units are contaminated with infectious organisms, with septic reactions occurring in approximately 1:250 000 units transfused. Infectious agents typically are gram-negative bacteria, most commonly *Yersinia enterocolitica*.
  - Platelets: approximately 1:1000 units of whole blood-derived and 1:5000 units of apheresis-derived platelets are contaminated with infectious organisms, with septic reactions occurring in approximately 1:250 000 whole blood-derived and about 1:108 000 apheresis-derived units transfused. Infectious agents typically are gram-positive bacteria such as staphylococci, streptococci, and gram-positive bacilli.
  - Plasma and cryoprecipitate: rare reports of endocarditis and mediastinal wound infections. Infectious agents typically are *Burkholderia cepacia* and *Pseudomonas aeruginosa*.
- Treatment:
  - Broad spectrum antibiotics covering suspected organisms, narrowed based on susceptibilities if available.
  - Supportive care and vasopressors as needed.

Transfusion-related acute lung injury (TRALI)

- Onset: 0–6 hours after transfusion.
- Presentation: sudden onset of respiratory distress with hypoxemia, dyspnea, tachypnea, and bilateral lung infiltrates, typically with fever, tachycardia, or hypotension.
- Incidence:
  - Unknown incidence.
  - Associated with all blood products, but increased risk in plasma-containing products (plasma and platelets).
  - Mortality rate of 15–20%.
- Prevention: dependent on preparation of blood product.

- Treatment:
  - Immediately stop transfusion.
  - Report to transfusion service.
  - Supportive care with intubation, mechanical ventilation, fluids, and vasopressors as needed.
  - Clinical improvement typically occurs after 48–96 hours.

Transfusion-associated circulatory overload (TACO)

- Onset: 0–6 hours after transfusion.
- Presentation: dyspnea, orthopnea, cough, chest tightness, cyanosis, hypertension, congestive heart failure, headache.
- Incidence:
  - Estimated up to 1% of transfusions, but likely under-reported.
- Prevention:
  - Volume-reduced blood products.
  - Slow transfusion of blood products.
- Treatment:
  - Stop transfusion.
  - Diuresis.
  - Phlebotomy in rare cases.

Potentially moderate acute reactions

Hypotension

- Onset: 0–15 minutes after start of transfusion.
- Presentation: sudden drop in systolic blood pressure (SBP) by ≥30 mmHg and SBP ≤80 mmHg.
- Treatment:
  - Discontinue transfusion.
  - Supportive care with IV fluids as needed.
  - Avoid use of bedside leukoreduction filters.

Metabolic derangements

- Onset: typically occurs after transfusion of large volumes of blood products.
- Hyperkalemia: treat with dextrose, insulin, calcium, sodium polystyrene.
- Hypocalcemia: treat with calcium infusion.
- Hypothermia: prevent by using blood warmers prior to infusion; can treat using a heating blanket.

Mild acute reactions

Fever

- Onset: typically 0–4 hours after transfusion.
- Presentation: fever and/or chills without hemolysis; severe reactions include increase in temperature by >2°C, headache, nausea, and vomiting.
- Diagnosis: made by exclusion of other causes of fever.
- Incidence:
  - Platelets: 0.4–2.2% in non-leukoreduced, 0.1–1.5% with leukoreduced platelets.
  - RBCs: up to 6.8% with non-leukoreduced, reduced with leukoreduced RBCs.
  - Plasma: approximately 0.02%.
- Prevention:
  - Use of leukoreduced blood products.
  - Removal of plasma from platelet products.
  - Unclear if premedication with acetaminophen and diphenhydramine is beneficial.

- Treatment:
  - Discontinue transfusion.
  - Antipyretics (acetaminophen 325–650 mg is preferred agent).
  - Meperidine 25–50 mg IV for rigors (avoid with renal failure and MAOI therapy).

Transfusion-associated dyspnea (TAD)

- Onset: 0–24 hours after transfusion.
- Presentation: respiratory distress that does not meet criteria for TRALI, TACO, or allergic reaction and is not explained by another medical condition.
- Treatment:
  - Discontinue transfusion.

Delayed post-transfusion complications

- Onset within days:
  - Delayed hemolytic reactions.
  - Alloimmunization.
  - Transfusion-transmitted diseases.
- Onset within weeks:
  - Transfusion-associated graft-versus-host disease.
  - Post-transfusion purpura, moderate to severe.
  - Transfusion-related immunomodulation.
- Onset within years:
  - Iron overload.

Reading list

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Additional material for this chapter can be found online at:
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This includes multiple choice questions.

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CHAPTER 55

Anticoagulation-Related Bleeding

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OVERALL BOTTOM LINE
- Anticoagulant agents are used to prevent and treat a wide range of cardiovascular, cerebrovascular, and thromboembolic diseases.
- The most important complication of treatment with anticoagulants is hemorrhage, which may be life threatening, and may cause long-term debilitating disease.
- If severe bleeding occurs or if a patient needs to undergo an urgent invasive procedure, such as emergency surgery, reversal of the anticoagulant effect may be required.
- Reversal of anticoagulation requires a careful and balanced assessment of the benefits and risks of such reversal.
- In certain cases, strategies should be utilized to keep the period of reversal as short as possible.

Background

Definition of disease

- Major bleeds are those that result in death, are life threatening, cause chronic sequelae, or consume major health care resources.
- Criteria for major bleeding in non-surgical patients are:
  - Fatal bleeding.
  - Symptomatic bleeding in a critical area or organ.
  - Bleeding causing a fall in hemoglobin level of 2.0 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.

Incidence/prevalence

- The risk of major bleeding with use of anticoagulation depends on several factors, including the agent used, indication for anticoagulation, intensity of anticoagulation effect, age, underlying comorbidities, concomitant medications, and duration of treatment (Table 55.1).
- Direct oral anticoagulants (DOACs) may be related to a higher risk of bleeding when used after hip surgery, acute coronary syndrome, or for thromboprophylaxis; but inversely cause less bleeding in patients with acute venous thromboembolism (VTE) or pulmonary embolism (PE).
- Collectively and individually the DOACs may cause equal or even less major bleeding when compared with vitamin K antagonists.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

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Table 55.1 Rates of major hemorrhage on vitamin K antagonists or heparin (per year).

Indication for anticoagulation therapy	Rates of hemorrhage
Prosthetic heart valves	1–19.2%
Atrial fibrillation	0–7%
Acute ischemic coronary syndrome	0–6.8%
Ischemic heart disease (long term)	0.6–14.5%
Venous thromboembolism (initial treatment)	0–7.0%
Venous thromboembolism (long term)	0–16.7%

Etiology

- Anticoagulants, such as warfarin, heparin, direct thrombin inhibitors, factor Xa inhibitors, and antiplatelet agents are used for a variety of indications, including treatment and prophylaxis of VTE, stroke prevention in atrial fibrillation, ischemic cerebrovascular disease, and cardiovascular disease.
- Bleeding is a major complication of these agents in the setting of poor drug monitoring, advanced age, multiple patient comorbidities, drug–drug interactions, and trauma.
- Intracranial hemorrhage, gastrointestinal (GI) bleeding, and trauma-related bleeding are some of the common consequences of bleeding secondary to anticoagulation.

Pathology/pathogenesis

- Coumarins/vitamin K antagonists (VKAs):
  - Vitamin K is a cofactor for the carboxylation of glutamate residues of vitamin K-dependent coagulation factors (factors II, VII, IX, and X) that require carboxylation for their biologic activity.
  - By inhibiting vitamin K, coumarins cause hepatic production of partially carboxylated and decarboxylated coagulation factors with reduced procoagulant activity.
- Heparin:
  - Unfractionated heparin (UFH) binds to antithrombin III to irreversibly neutralize thrombin and factor Xa.
  - Low molecular weight heparin (LMWH) is produced from UFH by chemical or enzymatic depolymerization. It efficiently inactivates factor Xa and, to a lesser degree, thrombin.
- Factor Xa inhibitors:
  - Oral factor Xa inhibitors exert their anticoagulant effect by preventing factor Xa-dependent conversion of prothrombin to thrombin.
  - Three oral factor Xa inhibitors are currently available for clinical use: rivaroxaban, apixaban, and edoxaban.
  - Oral factor Xa inhibitors directly bind to the active site of factor Xa, thereby inhibiting both free and clot-associated factor Xa.
  - Indirect Xa inhibitors, such as fondaparinux, bind to antithrombin III to inhibit factor Xa without having any effect on factor IIa.
- Direct thrombin inhibitors (DTIs):
  - DTIs competitively and reversibly bind to the active site of free and clot-bound thrombin, thereby blocking its pro-coagulant activity.
  - Available DTIs include dabigatran (oral), bivalirudin (intravenous), desirudin (subcutaneous), argatroban (intravenous), and lepirudin (intravenous).

- Antiplatelet agents:
  - Several classes of FDA-approved antiplatelet agents exist, including: aspirin, COX inhibitors, adenosine diphosphate receptor inhibitors, glycoprotein IIB/IIIA antagonists, and protease-activated receptor-1 antagonists.
  - The average lifespan of a platelet is 8–20 days. Thus, the effects of irreversible platelet inhibitors can be long lasting.

Predictive/risk factors

- Intensity of anticoagulation effect.
- Older age.
- Comorbidities (hepatic/renal insufficiency).
- Common genetic polymorphisms (in the setting of VKA use).
- Concomitant use of drugs interfering with hemostasis.
- Length of anticoagulation.
- Presence of malignancy.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- For patients on anticoagulation, therapeutic drug monitoring (for VKA/heparin), patient education, and routine monitoring of renal and hepatic function in patients with chronic liver and renal insufficiency are key to prevent hemorrhagic complications of these medications.

Drug monitoring

- VKA/heparin:
  - In the setting of VKA and heparin, the intensity of the treatment is strongly associated with the risk of bleeding. Therefore approaches to improve anticoagulation control by frequent point-of-care testing and minimizing INR/PTT fluctuations can improve the safety and effectiveness of these drugs.
- DOACs:
  - DTIs: thrombin time can be useful to determine the level of coagulopathy for DTIs.
  - Factor Xa inhibitors:
    - There are no specific laboratory parameters to monitor the anticoagulant impact of factor Xa inhibitors.
    - Antifactor Xa levels were originally designed and calibrated for LMWH; however, they can also be used to monitor or confirm overdose of factor Xa inhibitors. This test must be specifically calibrated for factor Xa inhibitors, as the results of the antifactor Xa level is assay specific.

Primary prevention

- It is important to educate patients on dietary restrictions and common OTC drug interactions.
- Use of an anticoagulant is associated with an increased risk of trauma-associated bleeding. Patients who elect to participate in activities with a greater than average risk for blunt trauma should be aware of the risks of bleeding.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- Common bleeding complications of anticoagulation include spontaneous intracranial hemorrhage, upper GI bleeding, diverticular bleeding, retroperitoneal bleeding, and trauma-related bleeding.
- A diagnosis of massive bleeding in the setting of anticoagulation can be made by careful clinical history, physical examination, and detailed medication reconciliation.
- Patients with hemorrhage can present with unstable vital signs, altered mental status in the setting of an intracranial bleed, internal or external hematomas, or hematemesis, melena, or hematochezia with a GI bleed.
- Following stabilization, diagnostic investigations include routine labs with a full coagulation profile, focused assessment using sonography for trauma (FAST) by ultrasound, and CT scanning or endoscopy depending on the source of the bleed.

Differential diagnosis

Differential diagnosis	Features
DIC: seen in association with underlying conditions such as: • Sepsis • Malignancy • Trauma • Obstetric emergencies • Transfusion reactions	Microangiopathic changes on peripheral blood smear (schistocytes) Thrombocytopenia, prolonged PT/aPTT, low fibrinogen, elevated D-dimer Low factor VIII levels Thromboembolic manifestations
Severe liver disease: • Acute hepatitis • Cirrhosis	Abnormal liver function tests Elevated PT/aPTT/INR, thrombocytopenia Normal or increased factor VIII levels

Typical presentation

- In the setting of supratherapeutic anticoagulation levels, patients typically present with a source of bleeding and abnormal laboratory values including decreased hematocrit and coagulation cascade abnormalities. In addition to visible sources of bleeding, patients may present with altered sensorium, orthostatic hypotension or hemorrhagic shock.

Clinical diagnosis

History

- History of recent trauma, upper or lower GI bleeding, syncopal episodes, headaches, vomiting, decreased level of consciousness, seizures.
- Past medical history to delineate need for anticoagulation (prior stroke, atrial fibrillation, MI, VTE).
- Medication reconciliation to evaluate for medication interactions that would inhibit metabolism of the anticoagulant in use.

Physical examination

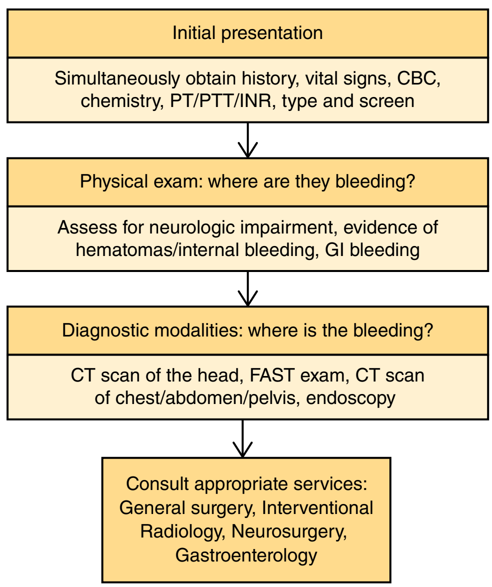
- Vital signs to assess for tachycardia, hypotension, and orthostasis.
- Full neurologic examination.
- Body inspection to specifically evaluate for hematomas or trauma.
- Digital rectal exam to evaluate for GI bleeding.

Laboratory diagnosis

- All patients should have a full set of routine labs, including, but not exclusive of, CBC, INR/PT/PTT, bleeding time, and a type and screen.
- CT scan of the head if there is an abnormal neurologic exam, recent trauma or fall, or altered sensorium.
- CT scan of the chest/abdomen/thighs if there is a history of recent fall/trauma or suspicion for internal bleeding.
- Upper or lower endoscopy if there is evidence of GI bleeding.

Diagnostic algorithm (Algorithm 55.1)

Algorithm 55.1 Diagnosis of anticoagulant-related bleeding



Potential pitfalls/common errors made regarding diagnosis of disease

- An incomplete medical and medication history can lead to treatment errors in patients who present with hemorrhage, in the event that a reversal agent is available; and can lead to increased bleeding in patients undergoing procedures.

Treatment

Anticoagulant-related bleeding is a time-sensitive medical emergency in which all facets of care should be performed simultaneously.

Treatment rationale

- Therapeutic options for VKA reversal include:
  - Vitamin K: normalizes the INR by providing the necessary substrate to synthesize vitamin K-dependent coagulation factors. IV administration is most effective at rapid INR reversal (Table 55.2).
  - Fresh frozen plasma (FFP): contains all the coagulation factors and proteins present in whole blood and reverses the anticoagulant effects of VKAs by replacing clotting factors.

Table 55.2 Recommendations for managing elevated INRs or bleeding in patients receiving vitamin K antagonists.

Condition	Intervention
INR <5; no bleeding	Lower or omit dose and resume when INR is in therapeutic range
INR >5 or <9; no bleeding	Omit next 1–2 doses, resume when INR is in therapeutic range, or administer 1–2.5 mg PO vitamin K*. If INR is still high, give additional vitamin K
INR >9; no bleeding	Hold warfarin, give vitamin K 2.5–5 mg PO (expect INR to be reduced substantially within 24–48 hours), and use additional vitamin K if necessary
Serious bleeding at any INR elevation	Hold warfarin and give vitamin K 10 mg IV; supplement with FFP, PCC, or rVIIa, depending on the urgency of the situation. Vitamin K can be repeated every 12 hours
Life-threatening bleeding	Hold warfarin and give FFP, PCC, or rVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR

* In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously.

   - Prothrombin complex concentrates (PCCs): contain variable amounts of factors II, VII, IX, and X; proteins C and S; and heparin. The benefits of PCC include its fast preparation and reconstitution time, rapid INR reversal, small volume, and lower risk of infection as compared with FFP.
      - Three-factor PCC: consists primarily of factors II, IX, and X.
      - Four-factor PCC: more effective because of additional activated factor VII.
   - Recombinant factor VIIa (off label use): results in rapid INR reversal. However, it is expensive compared with other reversal strategies and has a high risk of both venous and arterial thrombosis.
- Unfractionated heparin:
   - Protamine sulfate binds heparin to form a stable salt.
   - The half-life of protamine is approximately 7 minutes whereas the half-life of UFH is 60–90 minutes. Therefore, the dosing of protamine should account for the amount of UFH infused over the preceding 2–3 hours.
- Low molecular weight heparin:
   - Currently, there is no reversal agent specific to LWMHs.
   - Protamine is widely utilized; however, its ability to reverse LMWH varies significantly.
- Direct thrombin inhibitors:
   - Oral-activated charcoal can be used within 2 hours of ingestion to remove the unabsorbed dabigatran pro-drug from the GI tract.
   - Idarucizumab:
      - This is a specific, neutralizing, monoclonal antibody fragment, which adheres to the thrombin-binding site of dabigatran.
      - It is the most specific and fastest reversal agent for dabigatran.
   - PCC or activated PCC can be administered if idarucizumab is unavailable, or if the hemorrhage is associated with a DTI other than dabigatran.
   - Due to its low protein binding (35%) and high rate of renal excretion, dabigatran can be removed by hemodialysis in patients with renal insufficiency if idarucizumab is not available.
- Factor Xa inhibitors:
   - Activated charcoal can be administered to patients who present within 2 hours of ingestion of an oral direct factor Xa inhibitor.

- Andexanet alfa:
  - This is an inactive recombinant activated factor Xa analog that competes with and dilutes the activity of factor Xa, which converts prothrombin to thrombin.
- Antiplatelet agents:
  - Platelet transfusion.
  - Desmopressin.

When to admit to the ICU

- Active hemorrhage.
- Hemodynamic instability.
- Encephalopathy or altered mental status.

Managing the hospitalized patient

- Use the HASHTI mnemonic:
  - *H*old further doses of anticoagulant.
  - Consider *A*ntidote.
  - *S*upportive treatment: volume resuscitation, inotropes.
  - *H*emostatic measures: local or surgical.
  - *T*ransfusion: blood products.
  - *I*nvestigate for bleeding source.

Table of treatment

Treatment	Comments
Conservative Hold further doses of anticoagulants Monitor CBC Blood transfusions Supportive care	For non-life-threatening bleeding
Medical VKA antagonists: • Vitamin K 10 mg IV • FFP 4–6 units • PCC 25–50 IU/kg based on INR Heparin and LMWH: protamine 1 mg IV per 100 units UFH administered over the last 2–3 hours Factor Xa antagonists: andexanet alfa Dabigatran: idarucizumab 5 g IV, hemodialysis Antiplatelet agents: platelets, desmospressin 0.3 μg/kg IV	Dose of FFP and PCC depends on the INR of the patient and the severity of bleeding Andexanet alfa dosing – low dose: • Initial IV bolus: 400 mg IV; target infusion rate of 30 mg/min • Follow-on IV infusion: 4 mg/min IV for up to 120 minutes Andexanet alfa dosing – high dose: • Initial IV bolus: 800 mg IV; target infusion rate of 30 mg/min • Follow-on IV infusion: 8 mg/min IV for up to 120 minutes

Prevention/management of complications

- Caution should be exercised before using reversal agents in patients with concomitant life-threatening ischemia, thrombosis, or severe DIC because of the possibility of provoking thrombosis and ischemia.
- FFP administration carries complications such as pulmonary edema and intravascular volume overload, as well as transfusion-related reactions such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO).

- PCCs should be used with caution in patients who have evidence of acute arterial thrombosis, DIC, or other coagulopathic states. Because of the rapid reversal action of PCC, a follow-up INR can be checked within 15–60 minutes of administration.
- Recombinant factor VIIa has been associated with a relatively high thrombosis rate (12.8–24%), likely due to the procoagulant state and thrombin burst associated with higher doses. Patients with a concomitant hypercoagulable state or vascular injury are at higher risk of thrombotic complications, particularly arterial thrombosis. Use in anticoagulant-related bleeding is off label.
- Excessive protamine administration may exacerbate bleeding since protamine itself is a weak anticoagulant. Adverse reactions (anaphylaxis, hypotension, bradycardia, bronchoconstriction) are dose dependent but can be attenuated by slowing the infusion.

CLINICAL PEARLS

- The following reversal agents are available for rapid reversal of anticoagulants:
  - Vitamin K antagonists: vitamin K, FFP, and/or PCCs.
  - Heparin: protamine.
  - Dabigatran (direct thrombin inhibitor): idarucizumab or hemodialysis.
  - Antiplatelet agents: platelet transfusions and/or desmopressin.
  - Factor Xa inhibitors: andexanet alpha.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- The overall prognosis for a patient with an anticoagulation-related bleeding event depends on several factors, such as:
  - Major hemorrhage or minor hemorrhage.
  - Hemodynamic stability.
  - Age.
  - Underlying comorbidities.
  - Source of bleeding and ability to obtain adequate source control.
- In general, in the setting of a major bleeding event, reversal of anticoagulation along with source control is likely to improve the overall prognosis if hemostasis is achieved.

Natural history of untreated disease

- Time to restoration of hemostasis after cessation of anticoagulation (times may vary depending on hepatic/renal function):
  - VKA: 60–80 hours.
  - Heparin: 3–4 hours.
  - LMWH: 12–24 hours.
  - Indirect factor Xa inhibitors: 24–30 hours.
  - Factor Xa inhibitors: 12 hours.
  - DTI: 12 hours.
  - Aspirin: 5–10 days.
  - Clopidogrel: 1–2 days.

Follow-up tests and monitoring

- Reversal of anticoagulation therapy can be followed by interval testing of coagulation tests such as PT, PTT, INR, and bleeding time until hemostasis is achieved.

Reading list

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Schulman S, Beyth RJ, Kearon C, Levine MN; American College of Chest Physicians. Hemorrhagic complications of anti-coagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133(Suppl 6):S257–98.

Guidelines

National society guidelines

Title	Source	Date and reference
Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage	Neurocritical Care Society and Society of Critical Care Medicine	2016 Neurocrit Care 2016;24(1):6–46
Pharmacology and Management of the Vitamin K Antagonists	American College of Chest Physicians	2008 Chest 2008;133(Suppl 6):S160–98

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 56

Coagulopathy and Thrombocytopenia

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OVERALL BOTTOM LINE

- Coagulopathy, whether defined as abnormal coagulation, excessive fibrinolysis, or defects of platelet function or number, is common in critically ill patients and is associated with poor outcomes.
- A swift and thorough search to identify the primary cause, incorporating the clinical history, physical exam, and pattern of laboratory abnormalities, is crucial to manage the coagulopathic patient as varying etiologies require different treatment strategies.
- Routine correction of laboratory abnormalities with blood products in asymptomatic patients should generally be avoided, unless the patient is at high risk of bleeding.

Background

Definition of disease

- A *coagulopathy* is a state of abnormal hemostasis in which an individual's ability to form a clot to reduce bleeding is impaired, thereby increasing the bleeding risk; however coagulopathy may also describe prothrombotic states.
- Coagulopathy is characterized by abnormalities on tests assessing hemostasis: most commonly manifesting in the prothrombin time (PT), which monitors the tissue factor pathway, the activated partial thromboplastin time (aPTT), which monitors the contact activation and common pathways, and platelet count. The term coagulopathy is often meant to describe abnormalities in the PT and aPTT, while thrombocytopenia is used separately to distinguish a low platelet count. The PT, aPTT, and platelet count do not define the ICU patient's entire hemostatic state, however, as abnormalities in other coagulation assay abnormalities and disorders of platelet function are common.

Incidence/prevalence

- Coagulopathy in critically ill patients is common but the incidence and prevalence vary widely depending on the patient population studied and the cutoffs used to define a coagulopathic state.
- An international normalized ratio (INR) >1.5 occurs in nearly 60% of critically ill patients.
- Thrombocytopenia as defined by a platelet count of $<150 \times 10^9$/L occurs in up to 60% of patients, although severe thrombocytopenia ($<50 \times 10^9$/L), the point at which bleeding risk increases exponentially, is much less common.

Etiology

In the majority of critically ill patients, deficiencies of coagulation factors and thrombocytopenia are acquired.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Coagulopathy

- Disseminated intravascular coagulation (DIC), a condition of systemic intravascular activation of coagulation marked by consumption of coagulation factors, is the most common cause and can be secondary to many conditions, including sepsis, malignancy, and trauma.
- Because the liver produces all clotting proteins except for factor VIII, liver disease is a common cause of dual pathway abnormalities.
- The synthesis of factors II, VII, IX, and X are all dependent on vitamin K, which is frequently deficient in ICU patients due to inadequate intake and alterations in microbial synthesis due to antibiotic exposure. Vitamin K deficiency also causes dual pathway abnormalities, and can be distinguished from liver disease by measuring factor V levels, as factor V synthesis is not vitamin K dependent.
- Losses of coagulation factors in the setting of hemorrhage without replacement (e.g. crystalloid/colloid resuscitation) will lead to dilutional coagulation defects.
- Anticoagulants are common in the ICU, and depending on the underlying anticoagulant used, will variably affect tests of hemostasis.
- Inherited factor deficiencies or the presence of inhibiting antibodies are seen less commonly in ICU patients.

DIC scoring system

Laboratory test	Points
Platelet count (× 10^9/L)	
>100	0
<100	1
<50	2
Prothrombin time	
<3 seconds	0
>3 and <6 seconds	1
>6 seconds	2
Fibrinogen	
>1 g/L	0
<1 g/L	1
Fibrin degradation products	
↔	0
↑	2
↑↑	3
Total score	≥5 points is compatible with DIC

Thrombocytopenia

- Thrombocytopenia in the critically ill is caused by sepsis and DIC in 75% of cases, massive blood loss in 10%, and drug-related thrombocytopenia (including heparin-induced thrombocytopenia (HIT)) in 10%.
- Drug-induced thrombocytopenia can be due to immune-mediated mechanisms or direct myelosuppression. Many drugs have been implicated and lists are available online (http://www.ouhsc.edu/platelets/ditp.html).
- HIT is a life-threatening condition characterized by platelet-activating antibodies recognizing complexes bound to heparin–platelet factor 4 complexes. Classically, the fall in platelets is greater than 50% from

Table 56.1 Pathogenesis of common causes of acquired coagulopathies in critically ill patients.

Mechanism	Syndrome
Impaired synthesis	Liver insufficiency Vitamin K deficiency
Consumption of coagulation factors	DIC, sepsis, trauma
Loss of coagulation factors	Massive bleeding

baseline but not below 20×10^9/L and starts 5–10 days after heparin exposure. Heparin–platelet factor 4 antibodies are highly sensitive screening tests but require confirmation.

- Thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), malignant hypertension, and in obstetric patients the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome are responsible for about 1% of cases. These conditions have a similar pathogenic pathway of endothelial injury, platelet adhesion, and thrombin generation, with subsequent mechanical fragmentation of red blood cells, although treatment is vastly different among them.

Pathology/pathogenesis

Coagulopathy

- Clotting disorders occur by various mechanisms in the ICU, but generally fall into three main categories: impaired synthesis, consumption, and loss/dilution (Table 56.1).
- Anticoagulation agents variably alter coagulation pathways.
- Impaired synthesis:
  - Since most clotting factors are produced in the liver, hepatic disease will lead to underproduction of many clotting factors.
  - Vitamin K deficiency leads to underproduction of the vitamin K-dependent factors.
- Consumption:
  - Consumption leads to progressive depletion of clotting factors and is the predominant mechanisms of coagulopathy in DIC, sepsis, and trauma.
- Dilution:
  - Dilution usually occurs in the setting of the massively hemorrhaging patient who is resuscitated without replacement of clotting factors.

Thrombocytopenia

- Thrombocytopenia in the ICU is often multifactorial, but one of four mechanisms usually predominates: increased consumption, underproduction, dilution, and sequestration (Table 56.2).
- Consumption/destruction: this is the most common cause of thrombocytopenia in the ICU. It occurs via two mechanisms: immune or non-immune mediated:
  - Immune-mediated thrombocytopenia occurs via the production of platelet antibodies and their subsequent destruction. In the ICU, it is commonly secondary to drugs, especially heparin, but can also be due to viral infections.
  - Non-immune mechanisms occur in patients with DIC, patients on cardiopulmonary bypass, and those with microangiopathic hemolytic anemias (MAHAs). TTP-HUS is rare in the ICU, but important to recognize as, left untreated, it can be fatal in >90% of patients. TTP is due to an acquired or hereditary insufficiency of von Willebrand factor cleaving protease (ADAMTS-13), leading to large von Willebrand factor multimers and platelet aggregation. HUS is caused by a cytotoxin released from a specific *Escherichia coli* serotype.

Table 56.2 Pathogenesis of common causes of thrombocytopenia in critically ill patients.

Mechanism	Syndrome
Increased consumption/ destruction	
Immune mediated	Drugs (heparin, glycoprotein IIb/IIIa inhibitors, vancomycin), viral infections (varicella-zoster virus, cytomegalovirus, Epstein–Barr virus, hepatitis C virus), immune thrombocytopenic purpura
Non-immune mediated	DIC, HELLP, TTP, HUS, mechanical (aortic balloon pumps, mechanical valves)
Decreased production	Drugs (antibiotics, chemotherapy), toxins (alcohol), nutritional deficiencies (vitamin B12, folate), viral infection (HIV, parvovirus), bone marrow failure (myelodysplastic syndrome, aplastic anemia, paroxysmal nocturnal hemoglobinuria)
Dilutional	Hemorrhage, crystalloid infusion
Sequestration	Hypersplenism, portal hypertension (cirrhosis)

  - Decreased production: this is usually due to bone marrow suppression. Medications are the most common culprit and should be reviewed. Toxins, viral infections, and nutritional deficiencies are also common causes.
- Dilution: occurs in the setting of hemorrhage without adequate platelet replacement.
- Sequestration: occurs in the setting of hypersplenism. It is common in cirrhosis.

Prevention

BOTTOM LINE/CLINICAL PEARLS

- Prophylactic transfusion of fresh frozen plasma (FFP) or platelets to prevent the development of clotting deficiencies and thrombocytopenia, respectively, is not recommended.
- ICU-related coagulopathies and thrombocytopenia are usually not specifically preventable, but general avoidance of modifiable, predisposing factors, such as avoiding heparin in patients with HIT, is part of routine critical care.

Screening

- Platelet count, PT, and aPTT are screening tests that detect many coagulopathies and are part of routine testing in critically ill patients. Further diagnostic testing will be based on the pattern of lab abnormalities and clinical context.
- Patients on anticoagulation should have coagulation studies monitored per the specific drug protocol to avoid both under- and overtreatment.
- For patients receiving heparin in whom clinicians consider the risk of HIT to be >1%, platelet count should be performed every 2–3 days from day 4 to 14 after heparin is started.

Primary pmrevention

- Administration of FFP and platelets to prevent coagulopathies and thrombocytopenia from developing is not recommended.
- Routine transfusion of FFP to prevent bleeding in patients with acquired coagulopathies is not recommended.

- Trauma patients should receive early and fixed repletion of clotting factors with blood products to prevent the dilutional coagulopathy that can develop (e.g. a 1:1:1 ratio of PRBCs : platelets : FFP). Despite a lack of evidence, these findings have been extended to resuscitation efforts in post-surgical bleeding and gastrointestinal and obstetric hemorrhage. It is being evaluated in the North American Pragmatic, Randomized Optimal Platelets and Plasma Ratios study.
- Dietary intake of vitamin K may be inadequate in the critical care setting, but there is no high quality evidence for routine supplementation for critical care patients at risk for deficiency.
- Avoidance of drugs known to commonly cause thrombocytopenia is one method which may reduce the risk of thrombocytopenia, although the practice must be weighed against avoiding potentially necessary therapies. Use of low molecular weight heparins (LMWHs) in lieu of unfractionated heparin for routine venous thromboembolism prophylaxis leads to a lower odds ratio of thrombocytopenia, and may be cost effective.

Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- The history focuses on clues pointing to a pre-existing coagulopathic condition, either inherited or acquired, such as cirrhosis or anticoagulant use, and underlying etiologies, such as a trauma or a source of infection.
- The physical exam extends the search to detect underlying coagulopathic conditions, as well as searching for evidence of active or recent bleeding.
- A platelet count, PT, and aPTT are the most important tests to identify coagulopathies and thrombocytopenia. Further testing aims at identifying the underlying etiology.

Typical presentation

- Most critically ill patients will have minor coagulopathies that are asymptomatic and only noticed on routine blood tests. Those that manifest symptoms typically do so by bleeding, frequently with ecchymoses at puncture sites or frank hemorrhage.
- Certain conditions, such as antiphospholipid syndrome and HIT, demonstrate prolonged clotting times but actually predispose to thrombosis and may require anticoagulation, which highlights the importance of elucidating the underlying etiology.

Clinical diagnosis

History

- An important initial step in the critically ill patient with a coagulopathy is to assess if the patient has been receiving any anticoagulation.
- A past medical or family history may elucidate both inherited and acquired causes of abnormal bleeding, such as von Willebrand disease (vWD), hemophilia, cirrhosis, and vitamin K deficiency.
- It may be the critical condition itself or its treatment causing the coagulopathy. Sepsis, DIC, trauma, for example, all commonly cause coagulopathies and thrombocytopenia in the ICU, as do antibiotics, heparin, and hemorrhage.

Physical examination

- The physical exam should assess for any signs of bleeding. Clotting factor deficiencies cause joint and soft tissue bleeding, while thrombocytopenia usually causes mucocutaneous bleeding.

- Gastrointestinal bleeding can be confirmed by a rectal examination or a lavage via a nasogastric tube. Bleeding into a thigh or abdomen can be significant but may be clinically occult.
- The clinician should also look for underlying diseases that may predispose to coagulopathy, such as the physical exam findings that accompany cirrhosis, sepsis, and trauma. Skin necrosis in the setting of heparin exposure and thrombocytopenia should raise the suspicion of HIT.

Useful clinical decision rules and calculators

4T scoring system for HIT

'T'	Points		
	2	1	0
*T*hrombocytopenia (acute)	Platelet ↓ >50% and nadir >20 × 10^9/L	Platelet ↓ 30–50% or nadir 10–20 × 10^9/L	Platelet ↓ <350% or nadir <10 × 10^9/L
*T*iming (from first heparin dose)	Day 5 to 10	Unknown exposure, > day 10, or < day 1 (with heparin exposure 30–100 days ago)	< day 4 (no recent heparin exposure)
*T*hrombosis	Thrombosis, skin necrosis, anaphylactoid reaction	Progressive/recurrent thrombosis, erythematous skin lesion	None
o*T*her	None	Possible	Definite
Total score*	≥6: high score	4–5: intermediate score	≤3: low score

*A low score has a very high negative predictive value (97–99%) and is useful for ruling out HIT. The positive predictive value is 10–20% for intermediate and 40–80% for high scores, depending on the clinical setting.

Disease severity classification

- Since laboratory abnormalities of the clotting factor pathways correlate poorly with bleeding risk, there is no formal severity classification based on PT and aPTT levels.
- Thrombocytopenia is further subdivided into mild (<150 × 10^9/L), moderate (<100 × 10^9/L), and severe (<50 × 10^9/L). This is not specific to the ICU population and the correlation between platelet count and bleeding risk also varies according to the underlying etiology.

Laboratory diagnosis

Differential diagnosis of laboratory abnormalities of hemostasis

	INR/PT	aPTT	Fibrinogen	FDP	TT	Platelet count	Comments
Syndromes							
DIC	↑	↑	↓/↔	↑	↑	↓	MAHA, sepsis, malignancy, ↑LDH
TTP-HUS	↔	↔	↔	↔	↔	↓	MAHA, ↑LDH, diarrhea, AMS, AKI
HELLP	↔	↔	↔	↔/↑	↔	↓	MAHA, ↑LDH, ↑LFTs, pregnancy, HTN, proteinuria

(*Continued*)

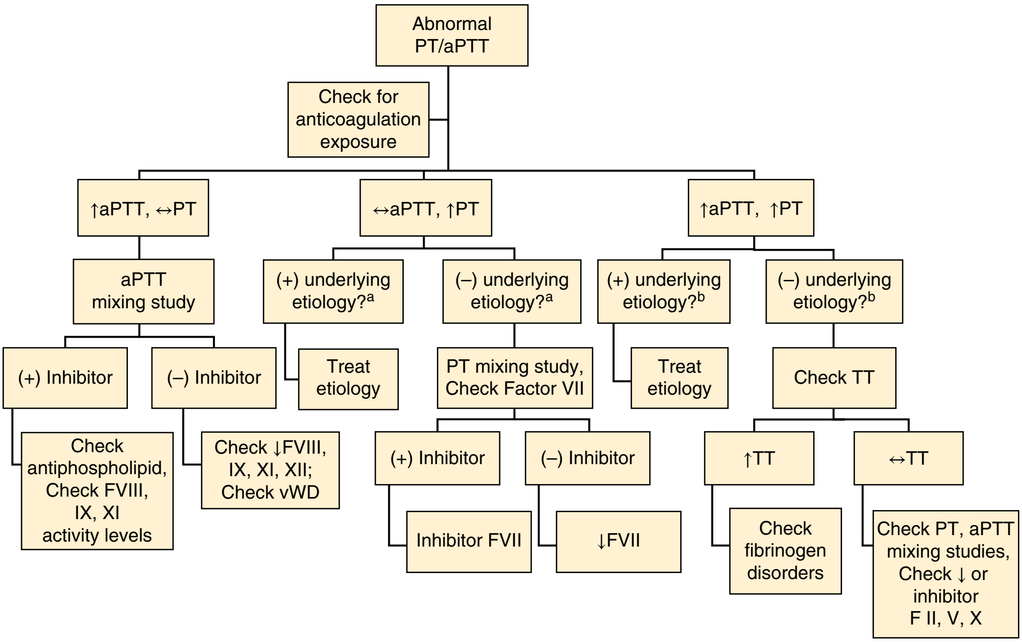
	INR/PT	aPTT	Fibrinogen	FDP	TT	Platelet count	Comments
Syndromes							
Liver disease							
Early	↑	↔	↔	↔	↔	↔	Normal factor VIII levels, cirrhosis
Late	↑	↑	↓	↑	↑	↓	
Dilutional	↑	↑	↔/↓	↔	↔/↑	↓	
Lupus anticoagulant	↔/↑	↑	↔	↔	↔	↔	Thrombosis
Vitamin K deficiency	↑	↑	↔	↔	↔	↔	↔aPTT if mild, normal factor V levels
Hyperfibrinolysis	↑	↑	↓	↑	↑	↔	
Platelet disorders							
von Willebrand disease (vWD)	↔	↑	↔	↔	↔	↔	↑BT
Uremia	↔	↔	↔	↔	↔	↔	Platelet dysfunction,↑BT
Drugs							
ASA/ thienopyridine	↔	↔	↔	↔	↔	↔	Platelet inhibitors, ↑BT
Coumadin	↑	↔/↑	↔	↔	↔	↔	↔aPTT early
UFH	↔	↑	↔	↔	↑	↔	↑PT when supratherapeutic
LMWH	↔	↔	↔	↔	↔	↔	Monitor anti-Xa activity assay, ↑PT when supratherapeutic
Direct thrombin inhibitors	↑	↑	↔	↔	↑	↔	Monitor aPTT
Factor Xa inhibitors	↔	↔	↔	↔	↔	↔	↑PT when supratherapeutic

AKI, acute kidney injury; AMS, altered mental status; aPTT, activated partial thromboplastin time; ASA, aspirin; BT, bleeding time; DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; HELLP, hemolysis, elevated liver enzymes, low platelets; HTN, hypertension; INR, international normalized ratio; LDH, lactate dehydrogenase; LFT, liver function test; LMWH, low molecular weight heparin; MAHA, microangiopathic hemolytic anemia; PT, prothrombin time; TT, thrombin time; TTP-HUS, thrombotic thrombocytopenic–hemolytic uremic syndrome; UFH, unfractionated heparin.

Abnormal PT/aPTT (Algorithm 56.1)

- Errors in sampling commonly cause abnormal clotting assays. This can be due to underfilling of the tube or using the wrong tube type. Repeating an unexpected test in accordance with proper collection technique will avoid costly and potentially invasive further testing.
- Exclude exposure to anticoagulation.
- If the aPTT is elevated and the PT is normal, an aPTT-based mixing study should be done to delineate the presence of an inhibitor to the contact activation pathway. In the setting of an inhibitor, the mixing study

Algorithm 56.1 Evaluation of abnormal PT/aPTT



[a] Vitamin K deficiency, liver disease. [b] Liver disease, disseminated intravascular coagulation, vitamin K deficiency, trauma, dilutional.

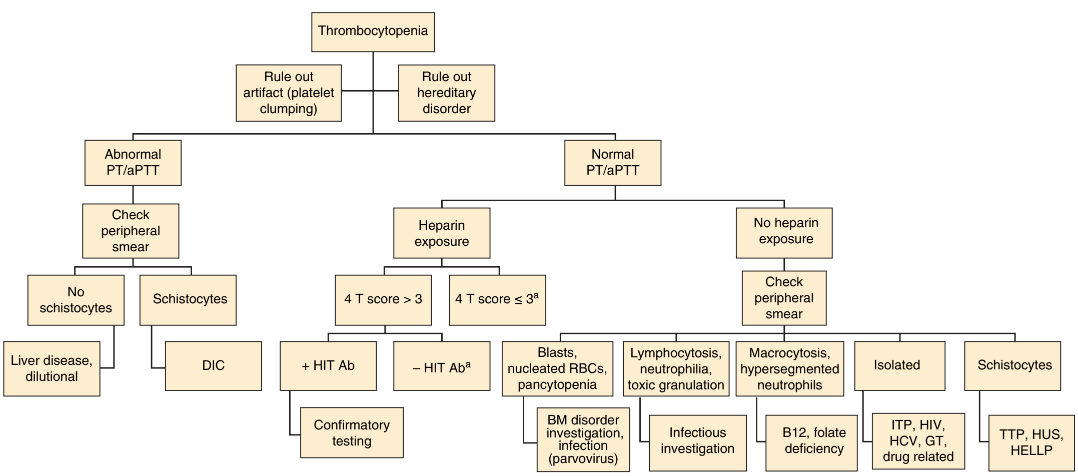
will not correct the aPTT, whereas the aPTT will normalize if there is a simple factor deficiency. Further testing for specific factor levels (VIII, IX, XI), antiphospholipid antibody testing, fibrinogen disorders, or vWD can be considered depending on such results.

- An isolated prolongation of the PT should prompt investigation of systemic disease, such as sepsis, DIC, early liver failure, or mild vitamin K deficiency. If there is no underlying etiology, a PT-based mixing study and factor VII activity will delineate the presence of an inhibitor or factor deficiency, which is rare.
- Likewise, prolongation of both the PT and aPTT warrants investigation of systemic disease, which is the most common cause. If none is found, a prolonged thrombin time will suggest fibrinogen disorders, while a normal thrombin time suggests factor inhibitors or deficiencies.

Thrombocytopenia (Algorithm 56.2)

- Pseudothrombocytopenia due to platelet clumping is common; consider redrawing with heparin- or citrate-containing collection tubes.
- The dynamics of the platelet count are particularly important in regards to HIT, which typically has its nadir between 5 and 10 days after heparin exposure.
- Thrombocytopenia should be interpreted in the context of other tests of coagulation; such as the PT, aPTT, fibrinogen, and fibrin degradation products, as well as a complete blood count.
- An examination of the peripheral smear should be an early step in the assessment of thrombocytopenia, with attention paid to all three cell lines.
  - White blood cells:
    - Leukemic cells diagnose hematologic malignancies.
    - Neutrophilia, lymphocytosis, and toxic granulation suggests infection.

Algorithm 56.2 Evaluation of thrombocytopenia



[a] HIT is unlikely. NB: the presence of coexisting disorders can alter the algorithm, e.g. a patient with cirrhosis who develops HIT. (Source: Adapted from Stasi 2012.) Ab, antibody; aPTT, activated partial thromboplastin time; BM, bone marrow; DIC, disseminated intravascular coagulopathy; GT, gestational thrombocytopenia; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver enzymes, and low platelets; HIT, heparin-induced thrombocytopenia; HIV, human immunodeficiency syndrome; HUS, hemolytic uremic syndrome; ITP, immune thrombocytopenic purpura; PT, prothrombin time; RBC, red blood cells; TTP, thrombotic thrombocytopenic purpura.

- Red blood cells:
  - Schistocytes indicate a MAHA. In the presence of other coagulopathies, consider DIC; otherwise, rule out TTP/HUS.
  - Macrocytosis suggests vitamin B12 or folate deficiency.
  - Dacrocytes (tear drop cells) suggest myelofibrosis.
  - Nucleated RBCs suggest hemolytic anemia, myelofibrosis, and infiltrative processes.
- Platelets:
  - Large platelets indicate increased turnover or hereditary disorders.
  - Small platelets are usually seen in production disorders.
- Isolated thrombocytopenia:
  - Drug-induced thrombocytopenia.
  - Viral-associated thrombocytopenia: parvovirus, hepatitis C, human immunodeficiency virus.
  - Connective tissue diseases.

General considerations

- Serum chemistry:
  - Creatinine elevation and uremia may identify renal failure, which is itself a risk factor for bleeding and may indicate diseases such as HUS.
- Liver function tests:
  - Abnormalities may support a diagnosis of cirrhosis and or the HELLP syndrome.
- Pregnancy test in pre-menopausal women.
- Blood cultures if sepsis and DIC are suspected.
- A type and screen should be drawn in case the patient will require blood product support.

Imaging techniques

- Abdominal ultrasound to assess for splenomegaly and cirrhosis.

Potential pitfalls/common errors made regarding diagnosis of disease

- PT and aPTT are relatively insensitive; both remain normal until factor levels are significantly depleted (<50%).
- The degree of PT and aPTT abnormalities does not necessarily correlate with the risk of bleeding, and may actually be indicative of a prothrombotic state.
- A positive HIT antibody should be interpreted only in the appropriate clinical context and confirmed with a serotonin-release assay or a heparin-induced platelet aggregation assay.
- Disorders of platelet function are common but are not reflected in platelet counts. This can occur due to medications (aspirin, glycoprotein IIb/IIIa inhibitors), renal disease, and intrinsic defects (vWD).

Treatment

Treatment rationale

- Many conditions in the ICU are associated with coagulopathies and thrombocytopenia. It is the responsibility of the clinician to not overtreat (i.e. unnecessary transfusions) while the primary etiology is being elucidated. The most common causes (e.g. DIC, sepsis, trauma) have no specific therapy and will improve with supportive care aimed at the underlying etiology.
- A platelet count threshold of 10×10^9/L is widely used as prophylaxis against spontaneous bleeding, but there is a lack of high quality evidence suggesting benefit. Avoiding prophylactic platelet transfusions at any level may be reasonable in patients with autologous stem cell transplantation.

Hemorrhage

- As mentioned previously, trauma patients should receive early and fixed repletion of clotting factors and platelets while receiving blood products to avoid dilutional coagulopathies and thrombocytopenia. There is an unproven benefit in other hemorrhaging patients, but most providers adhere to this practice.
- In non-massive hemorrhage, FFP should be transfused as long as the INR or aPTT is >1.5× the upper limit of normal. PCC can be given for patients in whom excessive volume is a concern and in patients on vitamin K antagonist therapy with intracranial bleeding.
- Platelets should be transfused to at least $>50 \times 10^9$/L; higher values may be necessary for high risk bleeding (e.g. intracranial).

Anticoagulation

- The management of a patient who presents with supratherapeutic clotting assays (e.g. a patient on warfarin who presents with an INR >3–3.5) but not actively bleeding may be difficult. The risk of bleeding with observation must be weighed against the risk of thrombosis if the patient is actively reversed. Those risks vary with the level of coagulopathy, patient comorbidities, and the condition being treated.
- If the bleeding risk is low, coagulopathies related to excessive anticoagulation can usually be observed.

Procedures

- Procedures are frequently necessary in the critical care patient, but coagulopathy is considered a relative contraindication to most procedures. Most simple procedures (e.g. central venous catheter placement) however appear to be safe with modest derangements of the PT and aPTT. Surgical and higher risk procedures will require input from the individual operator, and there is significant discrepancy among clinicians as to acceptable laboratory abnormalities.
- Minimum platelet counts for common ICU interventions are given in Table 56.3.

Table 56.3 Minimum platelet counts for common interventions in the ICU.

Platelet count ($\times 10^9$/L)	Procedure
10	Transjugular liver puncture, Central venous catheter placement
>20	Bone marrow biopsy, Gastrointestinal endoscopy with biopsy, Lumbar puncture (emergent), Bronchoscopy
>50	Bronchoscopy with biopsy, Lumbar puncture (elective), Spinal anesthesia
>80	Epidural anesthesia

Etiology-specific treatments

DIC	Coagulopathy and thrombocytopenia follow the clinical course of the disease and will resolve as the underlying condition improves There is no specific treatment. Therapy with intravenous heparin is controversial but not currently supported by clinical evidence
Sepsis	There is no specific treatment. Treatment is aimed at supportive care The Surviving Sepsis Campaign recommends that platelets be administered prophylactically when counts are $<10 \times 10^9$/L in the absence of bleeding, and $<20 \times 10^9$/L when at high risk of bleeding
Vitamin K deficiency	Coagulopathy will generally improve promptly with oral or intravenous administration of vitamin K

(*Continued*)

(*Continued*)

Factor deficiency/ inhibitor	Managing a critically ill patient with hereditary factor deficiencies or inhibitors is complicated and may require hematology consultation
Liver disease	Care is supportive In the setting of fulminant hepatic failure, no FFP is given unless there is active bleeding or need for invasive procedures
TTP	Early plasma exchange therapy improves outcomes; immunosuppressives (glucocorticoids, rituximab) are adjunctive therapies Transfusion of platelets only when bleeding
HUS	There is an unclear benefit of plasma exchange Eculizumab for complement-mediated HUS
HELLP syndrome	Delivery will usually lead to reversal within 72 hours Consider platelet transfusion for delivery if platelet counts <20 × 10^9/L
HIT	Stop all heparin (including LMWH and heparin flushes) once HIT is suspected Initiate treatment dose with fundaparinux, argatroban, lepirudin, or danaparoid, as dictated by comorbid conditions Transition to vitamin K antagonists once the platelet count is >150 × 10^9/L with a 5 day overlap Duration of anticoagulation therapy is unclear; most experts recommend 2–3 months in the absence of thrombosis
Drug-induced thrombocytopenia	Avoid future drug administration by documentation of allergy Intravenous immunoglobulin (in addition to platelet transfusions) can be considered if actively bleeding
Bone marrow suppression/failure	Treatment is supportive care and targeted to the underlying condition
ITP	Intravenous immunoglobulin and glucocorticoids if platelets <30 × 10^9/L and bleeding Glucocorticoids preferred over intravenous immunoglobulin in the non-bleeding patient

Special populations

CLINICAL PEARLS

- Coagulopathy and thrombocytopenia, while common, should always be investigated since delays in appropriate therapy for some conditions can lead to poor outcomes.
- In the bleeding patient, rapid reversal with product replacement is warranted.
- In the absence of etiology-specific therapy, treatment is supportive and the coagulopathy and thrombocytopenia will follow the clinical course. Routine transfusions are generally to be avoided.

Pregnancy

- Gestational thrombocytopenia is relatively common in pregnancy and is a diagnosis of exclusion. It is usually mild and no treatment is indicated.
- The HELLP syndrome is marked by hemolysis, liver function test abnormalities, and low platelets occurring in the third trimester. It is an obstetric emergency and usually resolves within 72 hours of delivery. Continued worsening beyond this time should prompt consideration of alternate diagnoses, such as TTP.
- Amniotic fluid embolism is a devastating condition occurring during pregnancy or shortly after delivery. It is thought to be due to amniotic fluid entering the maternal circulation and leading to massive inflammation and an anaphylactoid reaction that leads to cardiogenic shock and respiratory failure. DIC is a prominent finding in affected patients. Care is supportive but outcomes are poor.

Elderly

- The management of coagulopathy and thrombocytopenia in the elderly is the same as in any other adult patient.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Critically ill patients who have laboratory evidence of coagulopathy and/or thrombocytopenia have worse outcomes.
- Thrombocytopenia is a particularly important prognosticator in sepsis, especially if the thrombocytopenia persists beyond 4–7 days of ICU admission.
- It is unclear if coagulopathy directly contributes to these worse outcomes, or if it is merely a marker of disease severity. Increased mortality in thrombocytopenic and coagulopathic ICU patients is generally not due to increased bleeding events or an inability to achieve hemostasis.

Natural history of untreated disease

- Acquired coagulopathy and thrombocytopenia in critically ill patients usually improves following the course of critical illness since the most common etiologies are directly related to the critical illness.
- Those with pre-existing conditions or specific etiologies will remain coagulopathic unless the condition is treated.

Reading list

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Guidelines

National society guidelines

Title	Source	Date and reference
Guidelines on the Diagnosis and Management of Thrombocytopenic Purpura and Other Thrombotic Microangiopathies	British Committee for Standards in Haemotology	2012 Scully M, et al. Br J Haematol 2012;158:323–35

(*Continued*)

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Title	Source	Date and reference
Platelet Transfusion: A Clinical Practice Guideline From the AABB	American Association of Blood Banks	2015 Kaufman R, et al. Ann Intern Med 2015;162:205–13
Treatment and Prevention of Heparin-Induced Thrombocytopenia	Antithrombotic Therapy and Prevention of Thrombosis, 9th edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	2012 Linkins LA, et al. Chest 2012;141(Suppl 2):e495S–530S
Guidelines for the Diagnosis and Management of Disseminated Intravascular Coagulation	British Committee for Standards in Haematology	2009 Levi M, Toh CH, Thachil J, Watson HG. Br J Haematol 2009;145(1):24–33

International society guidelines

Title	Source	Date and reference
Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis	Surviving Sepsis Campaign Guidelines Committee	2012 Dellinger RP, et al. Crit Care Med 2013;41(2):580–637

Additional material for this chapter can be found online at:
www.wiley.com/go/mayer/mountsinai/criticalcare

This includes multiple choice questions.

CHAPTER 57

Venous Thromboembolism and Pulmonary Embolism

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OVERALL BOTTOM LINE

- Critical illness increases the risk of venous thromboembolism (VTE), making acute VTE events common in the ICU population.
- Risk factors for VTE events include venous stasis, hypercoagulable states, and endothelial injury.
- Maintaining high clinical suspicion is key to timely diagnosis and treatment.
- Classification into low risk, sub-massive, and massive pulmonary embolism is based on hemodynamic manifestations and not degree of radiographic clot burden.
- Treatment of acute pulmonary embolism is based on individual patient risk stratification.

Background

Definition of disease

- VTE is defined as a blood clot, or thrombosis, that forms in a vein which may or may not break off into emboli. In the critically ill, the most important manifestations are deep vein thrombosis (DVT) and acute pulmonary embolism (PE).

Disease classification

- DVTs can occur in any extremity, and when they occur in the lower extremity they are classified as distal if they involve the calf veins and proximal if they involve the popliteal, femoral, or iliac veins.
- Acute PEs can vary in size and location within the pulmonary vasculature but are classified by hemodynamic manifestations.
- Massive PE is defined as acute PE with hemodynamic instability (i.e. hypotension, shock, cardiac arrest), sub-massive PE is defined as acute PE without hypotension but with evidence of right ventricular dysfunction, and low risk PE is defined as acute PE not classified as either massive or sub-massive.

Incidence/prevalence

- Since DVT and PE represent a spectrum of one disease, there is a close relationship between incidence of DVT and PE in the ICU population.
- In the absence of mechanical and chemoprophylaxis, the incidence of DVT in the ICU varies from 10% to 30% in medical/surgical units versus up to 60% in trauma patients.
- With routine use of mechanical and anticoagulant prophylaxis, the risk of symptomatic DVT is as low as 1–12%.
- PE occurs in up to 50% of patients with a proximal DVT. Additionally, about 80% of patients who present with an acute PE have evidence of DVT in the legs.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

Companion website: www.wiley.com/go/mayer/mountsinai/criticalcare

Etiology

- Thrombi usually form in venous valve pockets or other sites of venous stasis. Although the specific etiology varies depending on the underlying disease state, there is a common theme of venous stasis, endothelial injury, and/or hypercoagulability that leads to clot formation.

Pathology/pathogenesis

- Thrombi that form in the deep veins of the lower extremities can propagate proximally. More proximal thrombi, especially above the popliteal level, are at higher risk for embolization.
- Thromboemboli travel towards the heart via the inferior vena cava, enter through the right side of the heart and continue into the pulmonary arteries.
- Depending on clot size, anatomic location, acuity of disease, and baseline cardiopulmonary reserve, the resultant pulmonary emboli can lead to a wide variety of clinical symptoms, ranging from being asymptomatic to dyspnea, hypoxemia, chest pain, hemodynamic collapse, and even sudden death.

Predictive/risk factors

- Risk factors for thrombi formation fall under three broad categories: venous stasis-promoting states, intrinsic hypercoagulable states, and direct injury or trauma.
- There are many acquired and hereditary factors that promote a hypercoagulable state, conferring an increased risk for VTE. For hospitalized patients, the risk is further compounded by additional factors such as immobility, acute medical illness, and possible surgical procedures.
- Important risk factors for VTE to consider in the critically ill population are listed here.

Patient population	Risk factor
Inpatient	Age >75 years
	Cancer
	Previous VTE
	Acute infectious disease
	Cranial surgery
	ICU patient
	Acute respiratory failure
	Surgery
	Indwelling central venous catheter
	Bedbound
	Chronic care facility
Community	Trauma
	Malignancy without chemotherapy
	Malignancy with chemotherapy
	Prior central venous catheter or transvenous pacing
	Neurologic disease with extremity paresis

Risk stratification

The ICU-VTE score can be used to classify critically ill patients as low, medium, or high risk for developing DVT, PE, or both (Table 57.1).

Table 57.1 ICU-VTE scoring system for risk of developing DVT and/or PE.

ICU-VTE score			Points
Baseline predictors			
Prior history of VTE			4
Platelet count on hospital admission >250 000/μL			1
In-hospital predictors			
Central venous catheterization			5
Bedbound ≥4 days			4
Invasive mechanical ventilation			2
Lowest hemoglobin level during admission ≥9 g/dL			2
Maximum total score			**18**
VTE risk category	**Total score**	**Risk of symptomatic VTE**	
Low	0–8 points	0.3%	
Intermediate	9–14 points	3.6%	
High	15–18 points	17.7%	

Prevention

Thromboprophylaxis against VTE is indicated and necessary for all hospitalized critically ill patients. The methods of prophylaxis range from mechanical (intermittent compression devices or compression stockings) to pharmacologic (unfractionated heparin or low molecular weight heparin), or a combination of both. The type of prophylaxis depends on the individual VTE risk for each patient.

Screening

Current guidelines recommend against routine screening for DVT in the critically ill population. Rather, several risk assessment models have been developed to categorize patients into low, medium, or high risk populations based on risk factors and to assist in deciding what kind of prophylaxis is most appropriate. Consensus statements recommend all hospitals formulate their own written guidelines for risk assessment of every inpatient.

Primary prevention

- The American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis clinical practice guidelines outline evidence-based practice recommendations for thromboprophylaxis in different medical settings.
- In general, pharmacologic prophylaxis with low dose unfractionated heparin (LDUH) and low molecular weight heparin (LMWH) has been shown to be effective and safe in medical patients. Both LDUH (5000 U SC either twice or three times daily dosing) and LMWH (enoxaparin 40 mg SC daily) reduce the risk of DVT and PE by more than 50%.
- Bleeding risk (e.g. in planned surgical procedure or acquired coagulopathy) is important to consider and may be a relative contraindication for anticoagulant prophylaxis. Other common contraindications include hypersensitivity to heparin products, heparin-induced thrombocytopenia (HIT), epidural anesthesia, hemorrhagic stroke, and renal insufficiency.
- Though less effective, the use of mechanical prophylaxis such as intermittent sequential devices or graduated compression stockings is recommended in addition to chemoprophylaxis, or alone if there is a contraindication to anticoagulant prophylaxis.
- Inferior vena cava (IVC) filters are not indicated for primary prophylaxis.

Secondary prevention

- DVT or PE recurrence occurs as a result of discontinuation of anticoagulation or from treatment failure.
- Duration of anticoagulation therapy differs depending on the mechanism of VTE formation. Provoked VTE events may only require therapy for a limited time whereas unprovoked VTE events may require lifelong anticoagulation.
- Because previous VTE is an independent risk factor for developing a new VTE event and risk of recurrence is high regardless of whether the VTE was provoked or unprovoked, clinical suspicion for recurrence must remain high.

Diagnosis

- Critical illness alone can lead to a hypercoagulable state, and combined with patient-specific risk factors, clinical suspicion must remain high for a hospitalized patient who becomes acutely critically ill.
- Classic exam findings for DVT include an asymmetrically swollen extremity, warmth, or tenderness. PE typically presents with acute onset pleuritic chest pain, dyspnea, tachycardia, or hypoxemia. It is important to note that in the critically ill, DVTs can remain asymptomatic and PEs can progress rapidly from minimal symptoms to hemodynamic collapse.
- CT angiography (CTA) is the gold standard for diagnosis of PE, but its use may be limited by a patient's medical stability or renal function. A ventilation–perfusion (V/Q) scan is an alternate testing option if renal function precludes CTA. Venous ultrasonography is the gold standard for DVT diagnosis and carries minimal risk.

Differential diagnosis

Differential diagnosis	Features
DVT	
Infectious cellulitis	Warm, tender, erythematous extremity; associated with fever and leukocytosis
Superficial thrombophlebitis	Pain, induration, erythema along course of a superficial vein
Lymphedema	Non-pitting edema with dermal thickening; assess for history of malignancy or lymph node dissection
PE	
Acute coronary syndrome	Pressure-like chest pain, elevated cardiac enzymes with ST abnormalities on ECG
Pneumothorax	CXR is diagnostic; bedside lung ultrasound shows absence of lung sliding
Pneumonia or thoracic mass	CXR with focal opacity or mass with obstruction; may present with infectious symptoms
Congestive heart failure	CXR with evidence of vascular congestion, elevated B-type natriuretic peptide (BNP)
COPD or asthma exacerbation	Wheezing on exam, improvement with bronchodilator or steroid therapy

Typical presentation

- A lower extremity DVT may present with asymmetric leg pain, warmth, or swelling; however, most DVTs are asymptomatic.

- Acute PE often presents with acute onset dyspnea or chest pain. Pleurisy and hemoptysis can also occur, and is commonly associated with pulmonary infarction.
- Massive PE manifests as hemodynamic instability and can lead to death.
- Signs and symptoms of DVT and PE are suggestive, but none are sensitive or specific. Thus, if suspicion is high, further diagnostic testing is required.

Clinical diagnosis

History

- It is important to ascertain any patient-specific comorbidities that may increase the risk for a VTE such as history of malignancy, prolonged immobility, or recent trauma.
- A personal history of prior DVT or PE is most important as it confers one of the highest risks for a new VTE event.

Physical examination

- Physical exam features of DVT and PE are non-specific and non-diagnostic so it is important to perform further diagnostic testing in appropriate patients.
- For the diagnosis of acute DVT, the exam may show swelling and tenderness of the extremity but often there are no significant physical exam findings.
- The cardiac exam is important for initial assessment of acute PE because right ventricular (RV) strain from acute pulmonary hypertension is a serious complication. Exam findings include jugular venous distention, a loud P_2, RV heave, or a right-sided gallop. ECG abnormalities include sinus tachycardia, S1Q3T3 pattern, right bundle branch block, or right axis deviation.
- RV strain can also be assessed via bedside point-of-care echocardiography to qualitatively assess RV size and function.
- Acute PE can also cause acute obstructive shock which manifests as hypotension with cool extremities and a narrow pulse pressure.

Disease severity classification

- Once the diagnosis of acute PE has been made, it is important to risk stratify the patient into low, intermediate, or high risk categories in order to guide medical decision making.
- The pulmonary embolism severity index (PESI, https://www.mdcalc.com/pulmonary-embolism-severity-index-pesi) is a validated prognostic scoring system that predicts 30 day mortality and is useful to guide initial management of acute PE, particularly for the management of very low risk patients. This clinical prediction rule uses 11 patient characteristics that are independently associated with mortality to classify patients into five severity classes of increasing mortality.

PESI components

- Age.
- Gender.
- History of cancer.
- History of heart failure.
- History of chronic lung disease.
- Heart rate ≥110/min.
- Systolic blood pressure ≤100 mmHg.
- Respiratory rate ≥30.
- Temperature ≤36°C (96.8°F).
- Altered mental status.
- O_2 saturation <90%.

Laboratory diagnosis

List of diagnostic tests

- For the hospitalized or ICU patient, D-dimer for the diagnosis of DVT or PE is rarely useful, as it is often positive in patients with infection, cancer, trauma, or other inflammatory states.
- Important laboratory tests include B-type natriuretic peptide (BNP) and troponin levels as these are good surrogates for RV strain and cardiac ischemia, respectively. Presence of RV strain or cardiac ischemia increases the risk for acute decompensation and thus may affect decisions about therapy.
- A coagulation panel should also be obtained as a monitoring parameter for anticoagulation initiation.

List of imaging techniques

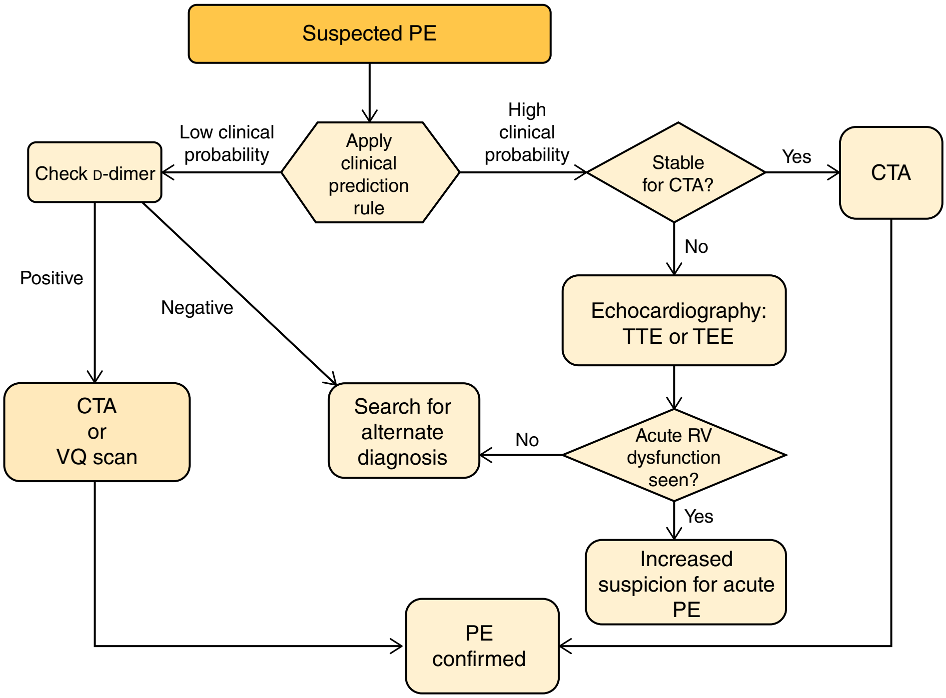
- Imaging is crucial to the diagnosis of VTE. The choice and timing of imaging modality is dependent on the stability of the patient.
- In general, *venous ultrasonography* is the gold standard for DVT diagnosis and *CTA* is the gold standard for PE diagnosis.
- In hemodynamically stable patients with high risk for PE, a CTA is sufficient for diagnosis as it has a very high negative predictive value of 95%.
  - If CTA cannot be done due to contraindication to intravenous contrast (i.e. allergic reaction or renal insufficiency), a V/Q scan is an alternative. A V/Q scan also has a high negative predictive value of 97%, but is diagnostic in only 30–50% patients with suspected PE.
  - If suspicion for PE is high with known DVT found on venous ultrasonography, then CTA can be avoided and treatment can be initiated.
- In hemodynamically unstable patients with suspicion for PE, CTA is the imaging modality of choice.
  - Clinical stability may limit timing or ability of obtaining CTA; therefore, transthoracic echocardiography (TTE) is an important adjunct imaging technique.
  - TTE is useful to assess for RV strain in the setting of acute PE causing hemodynamic instability or shock.
  - Transesophageal echocardiography (TEE) can also be done to visualize emboli in the main pulmonary arteries.

Diagnostic algorithm (Algorithm 57.1)

Potential pitfalls/common errors made regarding diagnosis of disease

- In critically ill patients, accurate and timely diagnosis is vital. Given CT imaging is now available widely, clinicians have come to rely more heavily on CTA for diagnosis, but there are many pitfalls in CTA.
  - Timing of imaging is a concern given the need to transport a patient to the scanner. Often, in the ICU setting, a patient's clinical stability may preclude safe transport.
  - ICU patients often have renal insufficiency that also precludes CT imaging.
- Bedside ultrasound in the form of point-of-care echocardiography and lower extremity venous compressive ultrasound are excellent adjuncts to aid in diagnosis, and are often underutilized.
  - Bedside ultrasound can be readily done, presents very little risk to the patient, and gives real time data that can rapidly inform treatment decisions.

Algorithm 57.1 Diagnostic algorithm for suspected pulmonary embolism



Treatment

Treatment rationale

- The mainstay of treatment for VTE is systemic anticoagulation.
- For hospitalized patients, LMWH or unfractionated heparin (UFH) is most commonly used as first line treatment as it has a relatively short half-life and can reach therapeutic levels within a few hours.
- For patients with high clinical suspicion for VTE, empiric anticoagulation (usually with UFH) should be started while awaiting results from diagnostic tests.
- In patients presenting with hemodynamic instability or shock, initiation of vasopressors and inotropes is indicated.
  - The preferred vasopressor is norepinephrine and the preferred inotrope is dobutamine.
  - It is prudent to avoid excessive intravenous fluid administration as it may worsen RV function and lead to further hypotension and clinical decline.
- Systemic thrombolytic therapy is indicated in patients with acute PE and hemodynamic instability.
  - For patients who are hemodynamically unstable or in cardiac arrest, systemic thrombolysis is indicated.
  - For patients who are hemodynamically stable, but with evidence of significant RV dysfunction, the decision for thrombolytic therapy should be made on a case by case basis by a multidisciplinary team. Low dose, catheter-directed thrombolysis has been shown to be effective in this population, but evidence is limited.
- In patients presenting with shock or cardiac arrest, surgical pulmonary embolectomy may be indicated if there is contraindication to thrombolysis or failure of thrombolysis (Figures 57.1 and 57.2).
- IVC filters are indicated when there is an absolute contraindication to anticoagulation or with treatment failure. IVC filters should not be routinely used as first line therapy.

Table of treatment for PE

Treatment	Comments
Medical	
Oral anticoagulation: • Rivaroxaban 15 mg twice daily ×21 days, then 20 mg daily • Coumadin individualized dosing for target INR 2–3 • Apixaban 10 mg twice daily ×7 days, then 5 mg twice daily	
UFH: • 5000 unit IV bolus, followed by 18 units/kg/h infusion • Target aPTT to institution protocol	
LMWH: • 1 mg/kg SC twice daily	LMWH and fondaparinux dosing is limited by renal function
Fondaparinux: • <50 kg: 5 mg SC daily • 50–100 kg: 7.5 mg SC daily • >100 kg: 10 mg SC daily	
Thrombolytic: • tPA 100 mg IV over 2 hours	Bleeding risk must be assessed when giving thrombolytic therapy
Low dose, catheter-directed thrombolysis: • Catheter placement via femoral vein into both right and left pulmonary arteries • Slow infusion of low dose thrombolytic via catheter localized to pulmonary arteries given over 15 hours	Low-dose, catheter-directed therapy is appropriate for patients with PE exhibiting hemodynamic stability and evidence of significant RV dysfunction, but given lack of strong evidence, decision should be made by multidisciplinary team
Surgical	
Pulmonary artery embolectomy: • Requires placing patient on emergent cardiopulmonary bypass • Open thoracotomy versus minimally invasive approach to access the main pulmonary arteries and retrieve clot	Appropriate for patients in cardiac arrest, refractory shock despite thrombolysis, or with contraindication to thrombolysis
IVC filter: • Placement in infrarenal IVC	

Prevention/management of complications

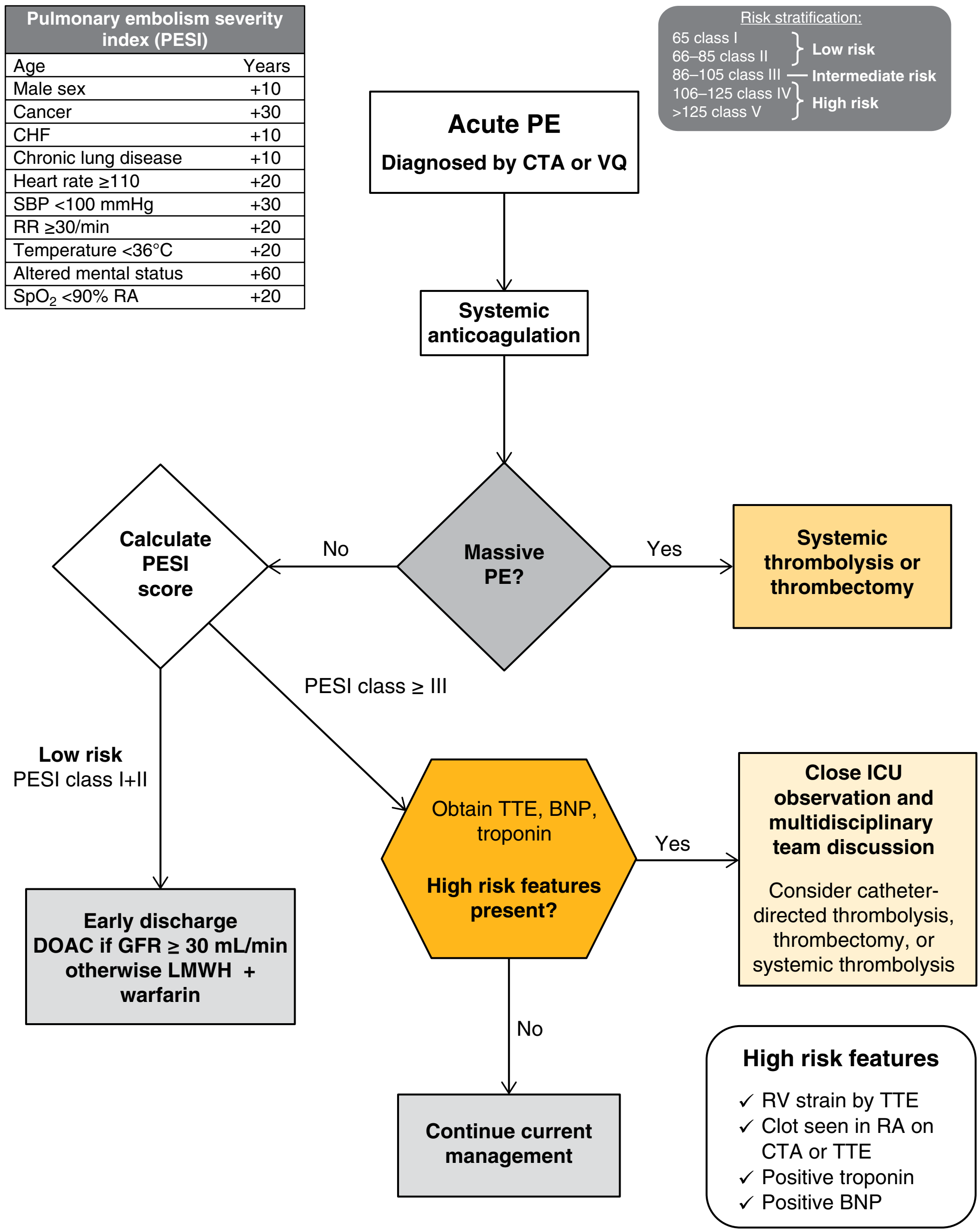
- The most important complication of VTE treatment is bleeding. Therefore, systemic anticoagulation requires frequent monitoring, especially in the ICU as critical illness can also promote coagulopathy. Additionally, UFH should be used when possible as it has a shorter half-life and can be reversed if necessary.
- HIT is a serious complication of heparin therapy and can lead to significant morbidity and mortality. Close monitoring of platelet count as well as coagulation factors is recommended.

Management/treatment algorithm (Algorithm 57.2)

CLINICAL PEARLS

- Systemic anticoagulation is the mainstay of treatment.
- High clinical suspicion for acute VTE necessitates empiric therapy while awaiting diagnostic testing.
- Early use of vasopressors and inotropes is indicated in the setting of shock.
- Thrombolysis is indicated in the setting of massive PE.

Algorithm 57.2 Management of acute PE



Special populations

Pregnancy

- Pregnant or post-partum women have a four-fold relative risk increase for VTE.
- The risk of a first episode of VTE is five times as high in the post-partum period than during pregnancy.
- Venous sonography should precede other imaging tests if there is suspicion for acute PE.
- The concern about radiation exposure should not deter clinicians from using CTA or V/Q scanning when there is suspicion for acute PE with clinical instability.
  - CT delivers a higher dose of radiation to the mother but a lower dose to the fetus than V/Q scanning.
  - Magnetic resonance angiography has been shown to have little utility in diagnosis.
- In the event of a life-threatening PE, thrombolytic therapy should not be withheld solely because of pregnancy.
- Warfarin is teratogenic and is contraindicated in pregnancy.

Elderly

- The risk of hemorrhage with thrombolysis, particularly intracranial hemorrhage, is significantly increased in patients older than 75 years.

Prognosis

BOTTOM LINE/CLINICAL PEARLS

- Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are possible long-term sequelae of DVT and PE, respectively.
- Recurrence rates are very high regardless of etiology of initial VTE event, and secondary prevention significantly reduces the burden of disease.
- Recurrence pattern generally mirrors the initial VTE event. For example, recurrence of PE is more common in patients with prior PE.

Prognosis for treated patients

- The 3 month overall mortality rate for patients with an acute PE who receive adequate anticoagulation has been reported to be 15–18%.
- Shock on presentation increases mortality by a factor of 3–7.
- Fewer than 5% of patients will develop chronic thromboembolic pulmonary hypertension after an initial PE.
- Post-thrombotic syndrome is the most common complication after DVT. Those with elevated D-dimer after completion of anticoagulation are at highest risk for developing post-thrombotic syndrome.

Follow-up tests and monitoring

- Repeat venography or CTA is not necessary to confirm clot resolution.
- After a sub-massive or massive PE, TTE can be used to follow-up resolution of RV dysfunction.
- If there is suspicion for development of chronic thromboembolic pulmonary hypertension, then a V/Q scan is the best imaging modality for diagnosis.

Reading list

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Guidelines

National society guidelines

Title	Source	Date and reference
ACCP Anticoagulation Guideline	American College of Chest Physicians	2016 Kearon C, et al. Chest 2016;149:315–52
AHA Statement: Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension	American Heart Association	2011 Jaff MR, et al. Circulation 2011;123(16):1788–830

Images

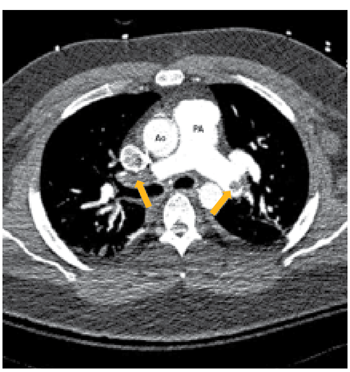

Figure 57.1 CTA image of a patient with bilateral massive PE who received systemic thrombolysis and emergent pulmonary artery embolectomy. Arrows indicate pulmonary emboli. Ao, aorta; PA, pulmonary artery. (Source: image from personal collection. Reproduced with permission from patient.)

Figure 57.2 Central pulmonary emboli fragments removed via pulmonary artery embolectomy from the same patient as in Figure 57.1. (Source: image from personal collection. Reproduced with permission from patient.)

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This includes multiple choice questions.

CHAPTER 58

Oncologic Emergencies

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OVERALL BOTTOM LINE

- Oncologic emergencies encompass a variety of clinical entities including tumor lysis syndrome, superior vena cava syndrome, neutropenic fever, and symptomatic leukostasis.

Background

Definition of disease

- Tumor lysis syndrome (TLS) involves massive tumor cell lysis releasing intracellular products into the systemic circulation causing electrolyte derangements including hyperkalemia, hyperphosphatemia, secondary hypocalcemia, and hyperuricemia, often leading to acute kidney injury.
- Superior vena cava syndrome (SVCS) results from obstruction of blood flow through the SVC, either by direct tumor invasion or extrinsic compression, thus causing edema and retrograde flow.
- Neutropenic fever is a single oral temperature of >38.3°C (101°F) or a temperature of >38°C (100.4°F) sustained for >1 hour occurring in a patient with neutropenia (absolute neutrophil count (ANC) <500 cells/μL), either from chemotherapy or direct myelodysplasia from cancer. It may be the only sign of infection in these immunosuppressed patients and is critical to recognize and act upon it to avoid worsening sepsis and potential death.
- Symptomatic leukostasis (SL) occurs in the setting of hyperleukocytosis, commonly seen in patients with acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) in blast crisis, in which leukocyte plugs in the microvasculature decrease tissue perfusion.

Incidence/prevalence

- TLS is most commonly associated with hematologic malignancies. The reported incidence rates for patients with non-Hodgkin's lymphoma, AML, and acute lymphoblastic leukemia (ALL) are 28%, 27%, and 19%, respectively.
- SVCS occurs in approximately 15 000 people in the USA every year. SVCS develops in 5–10% of patients with right-sided malignant intrathoracic mass lesions.
- Neutropenic fever most commonly occurs in patients undergoing chemotherapy; 10–50% in solid tumor and >80% in hematologic malignancies will develop fever associated with neutropenia during one or more chemotherapy cycles. An infectious etiology is only identified in 20–30% of febrile neutropenic episodes.

Mount Sinai Expert Guides: Critical Care, First Edition. Edited by Stephan A. Mayer, Janet M. Shapiro, Umesh K. Gidwani, and John M. Oropello.

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- The incidence of leukostasis varies by leukemia type; it affects up to 10–20% of patients with new AML and 10–30% of patients with new ALL.

Etiology

- TLS is most commonly induced by chemotherapy or radiation therapy. TLS also occurs spontaneously, typically in hematologic malignancies with high tumor cell proliferation rates and/or large tumor burdens (bulky disease or high WBC count).
- In SVCS, intrathoracic malignancy accounts for 60–85% of cases, along with other benign etiologies, such as thrombosis. Non-small cell lung cancer (NSCLC) is the most common malignant etiology, causing 50% of cases, followed by small cell lung cancer (SCLC) (25%) and non-Hodgkin's lymphoma (10%).
- Neutropenic fever is caused by immune suppression from the chemotherapy and directly from the underlying malignancy, which leads to higher susceptibility to various infections.
- SL occurs most commonly due to blast crisis in a patient with either AML or CML

Pathology/pathogenesis

- TLS occurs in malignancies (most commonly hematologic) with large tumor burdens, high cell proliferation rates, or high sensitivities to treatment.
  - Initiation of therapies (chemotherapy, radiation, and/or corticosteroids) can induce rapid lysis of tumor cells which causes massive release of intracellular components, such as potassium, phosphate, and nucleic acids (which are metabolized to uric acid). This ultimately can cause hyperkalemia, hyperphosphatemia, hyperuricemia, secondary hypocalcemia, and acute kidney injury.
- SVCS occurs due to obstruction caused by direct tumor invasion, external compression by processes involving the apical right lung, lymph nodes, or other structures in the mediastinum, or thrombosis.
  - As blood flow is obstructed, collateral venous circulation forms; however this process develops over several weeks and is generally insufficient for complete venous drainage, thus causing a marked elevation in upper body venous pressure.
  - Consequences of this include edema of the head and neck, which can lead to respiratory impairment (dyspnea, cough, stridor) and dysphagia. Life-threatening complications include cerebral edema and, rarely, hemodynamic compromise.
- Neutropenic fever is caused by both direct effects of chemotherapy on the immune system and on mucosal barriers as well as abnormalities in the host immune system due to the malignancy. The risk for specific types of infections is dictated by the specific type of immune deficit (humoral versus cellular).
- SL occurs due to increased blood viscosity from large leukemic blasts, exaggerated by cytokine leak and endothelial injury.

Prevention

Screening

- There are multiple forms of prevention for patients at high risk for TLS. High risk malignancies include Burkitt's leukemia, ALL and AML with WBC count >100 000/μL, stage III or IV lymphoblastic lymphomas, or any disease with a serum lactate dehydrogenase (LDH) level greater than two times the upper limit of normal.
- Patients at high risk for neutropenic fever are those expected to be profoundly neutropenic (ANC <100 cells/μL) for more than 7 days. Those with ongoing comorbidities including significant renal or hepatic dysfunction are also considered high risk.
- No screening exists for SVCS or SL.

Primary prevention

- The mainstay of prevention in patients at high risk for TLS is administration of aggressive intravenous hydration (2–3 L/m^2/day of IV fluid) as well as prophylactic rasburicase prior to initiation of treatment.
  - For those at intermediate risk, allopurinol should be given prophylactically as long as uric acid levels are not severely elevated (<8 mg/dL).
- The Infectious Disease Society of America guidelines recommend consideration of fluoroquinolone prophylaxis in patients at high risk for profound prolonged neutropenia (anticipated ANC ≤100 cells/μL for >7 days).
  - Prophylaxis against *Candida* is recommended in those undergoing allogeneic hematopoietic stem cell transplantation or intensive chemotherapy for leukemia. Prophylactic antibiotics are not recommended in low risk patients.
- No interventions have been demonstrated to prevent the development of SVCS or SL.

Secondary prevention

- Patients with a history of prior invasive fungal infections (particularly *Aspergillus*) are at high risk for recurrence with further chemotherapy.
- For patients with a history of prior invasive aspergillosis who receive myelosuppressive chemotherapy, voriconazole is recommended for secondary prophylaxis of disease reactivation.
- For patients with a history of *Candida* infections, secondary prophylaxis should be chosen based on prior susceptibilities. HSV-seropositive patients should receive acyclovir antiviral prophylaxis.

Diagnosis

Clinical diagnosis

History

- Regarding TLS, any history of a hematologic malignancy with a large tumor burden (either bulky disease >10 cm in diameter or WBC count >100 000/μL) is relevant. Symptoms associated with metabolic abnormalities, such as nausea, vomiting, diarrhea, fatigue, palpitations, muscle cramps, and syncope, should be sought out.
- Regarding SVCS, any history of lung cancer or lymphoma and any prior instrumentation involving the SVC are important. Dyspnea, cough, chest pain, dysphagia, and/or facial swelling and head fullness are common complaints.
- Patients at risk for neutropenic fever are those with anticipated prolonged (>7 days), profound neutropenia (<100 cells/μL). Patients with significant comorbidities, such as hypotension, pneumonia, abdominal pain, or neurologic changes, should be started on empiric antimicrobial therapy.
- Regarding SL, neurologic symptoms such as visual changes, headache, dizziness, tinnitus, and confusion are common. Pulmonary symptoms such as dyspnea should also be investigated.

Physical examination

- Patients with TLS should be evaluated for arrhythmias and tetany.
- In patients with neutropenic fever, a thorough evaluation for potential sites of infection including sinuses and oropharynx/dentition, a lung exam (pleural effusion, consolidation), a skin exam (abscesses, joint space infections), and an abdominal exam (any quadrant, suprapubic, or cerebrovascular accident tenderness) should be performed. Rectal exams must be avoided.
- Patients with SVCS should be evaluated for facial edema and erythema along with distension of the neck and chest wall veins. Arm edema, facial plethora, and cyanosis are also seen.
- Patients with SL may have an abnormal neurologic exam and hypoxia.

Useful clinical decision rules and calculators

- Clinical TLS is defined as laboratory TLS plus one or more of the following, not attributable to a therapeutic agent: increased serum creatinine (> than 1.5 times the upper limit of normal), cardiac arrhythmia/sudden death, or a seizure.
- Laboratory TLS is defined as any two or more abnormal serum values (uric acid >476 mmol/L or 8 mg/dL, potassium >6.0 mmol/L or 6 mEq/L, phosphorus >1.45 mmol/L or 4.5 mg/dL, calcium <1.75 mmol/L or 7 mg/dL) present within 3 days before or 7 days after instituting chemotherapy in the setting of adequate hydration and use of a hypouricemic agent.
- The Multinational Association for Supportive Care in Cancer (MASCC) score can be used to identify patients with neutropenic fever who are low risk for serious medical complications and poor outcome (Table 58.1). Those with a score <21 are high risk and should be admitted to the hospital or ICU for empiric antibiotics.
- The severity of TLS can be graded using the Cairo–Bishop clinical TLS grading scale (Table 58.2).
- The severity of SL can be graded on the basis of pulmonary, neurologic, or other organ system involvement (Table 58.3).
- The severity of SVCS can be graded based on the extent and severity of edema (Table 58.4).
- There are no risk scores for SVCS or SL.

Neutropenic fever

- High risk patients are those considered to be at high risk for serious complications during fever and neutropenia. They are defined as either those with a MASCC score of <21 or those who have any of the following criteria:
  - Profound neutropenia (ANC <100 cells/mm^2) anticipated to extend >7 days.
  - Hemodynamic instability.
  - Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhea.
  - Gastrointestinal symptoms, including abdominal pain, nausea and vomiting, or diarrhea.
  - Neurologic or mental status changes of new onset.
  - Intravascular catheter infection, notably catheter tunnel infection.
  - New pulmonary infiltrate, hypoxemia, or underlying chronic lung disease.
  - Evidence of hepatic insufficiency (defined as aminotransferase levels >5× normal values) or renal insufficiency (defined as a creatinine clearance of <30 mL/min).

Table 58.1 The MASCC risk index score.

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age <60 years	2

Table 58.2 Cairo–Bishop clinical TLS definition and grading.

	Grade					
Complication	**0**	**1**	**2**	**3**	**4**	**5**
Creatinine	≤1.5 x ULN	1.5 x ULN	>1.5–3.0 x ULN	>3.0–6.0 x ULN	>6.0 x ULN	Death
Cardiac arrhythmia	None	Intervention not indicated	Non-urgent medical intervention	Symptomatic and incompletely controlled medically or with device	Life threatening	Death
Seizure	None	-	One brief, generalized seizure; well controlled by anticonvulsants and/or not interfering with activities of daily living	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough with generalized seizure despite medical intervention	Seizure of any kind which is prolonged, repetitive, or difficult to control (e.g. status epilepticus)	Death

ULN; upper limit of normal activities of daily living.

Table 58.3 Probability of SL deduced from severity of symptoms.

Group	Probability of leukostasis syndrome	Severity of symptoms	Pulmonary symptoms	Neurologic symptoms	Other organ systems
0	Not present	No limitations	No symptoms and no limitations in ordinary activities	No neurologic symptoms	No symptoms
1	Possible	Slight limitations	Mild symptoms and slight limitation during ordinary activity	Mild tinnitus, headache, dizziness	Moderate fatigue
2	Probable	Marked limitations	Marked limitation in activity, even during less than ordinary activity	Slight visual disturbances[1], severe tinnitus, headache, or dizziness	Severe fatigue
3	Highly probable	Severe limitations	Dyspnea at rest; oxygen or respirator required	Severe visual disturbances[1] (acute inability to read), confusion, delirium, somnolence, intracranial hemorrhage	Myocardial infarction, priapism, ischemic necrosis

[1] Blurred vision, diplopia, hemianopia

Table 58.4 Grading system for SVCS.

Grade	Category	Estimated incidence (%)	Definition
0	Asymptomatic	10	Radiographic SVC obstruction in the absence of symptoms
1	Mild	25	Edema in head or neck, cyanosis, plethora
2	Moderate		Edema in head or neck with functional impairment (cough, mild dysphagia, visual disturbance)
3	Severe	10	Mild or moderate cerebral edema or laryngeal edema, diminished cardiac reserve
4	Life-threatening	5	Significant cerebral edema or laryngeal edema; significant hemodynamic compromise
5	Fatal	<1	Death

Note: Each sign or symptom must be thought due to SVC obstruction

Laboratory diagnosis

List of diagnostic tests

- In TLS, serologic testing with LDH, BMP (creatinine, potassium, calcium), and phosphorus is indicated.
- In neutropenic fever, one must obtain a CBC with differential, BMP, liver enzymes, at least two sets of blood cultures (with a set collected simultaneously from each lumen of an existing central venous catheter, if present, and from a peripheral venous site) as well as cultures from other sites as clinically indicated.
- In SL, PaO_2 can be falsely low (due to enhanced metabolic activity of malignant cells). Other important laboratory tests are a CBC with differential, BMP, and labs to evaluate disseminated intravascular coagulation. Pathologically, a biopsy of involved tissue will show white cell plugs in the microvasculature (rarely obtained).
- There are no diagnostic tests for SVCS.

List of imaging techniques

- When SVCS is suspected a CXR and a CT scan of the neck and chest should be obtained to evaluate for obstructing mass.
- In neutropenic fever, a CXR should be ordered to evaluate for possible pulmonary infectious etiology. Further imaging should be ordered as dictated by the clinical picture.
- There are no imaging techniques for TLS or SL.

Treatment

Treatment rationale

- The best treatment for TLS is prevention, employing continuous cardiac monitoring, serial laboratory evaluations (electrolytes, renal function, uric acid) every 4–6 hours, and rasburicase 0.2 mg/kg with repeated dosing as needed in high risk patients.
  - In those who develop TLS, the management is largely supportive and consists of correction of electrolyte abnormalities, aggressive hydration, and renal replacement therapy as indicated.
- There are multiple modalities used to treat SVCS, depending on the clinical situation (type of tumor, severity of symptoms, patient comorbidities/preferences) (Algorithm 58.1).

- In cases of neutropenic fever, broad spectrum antibiotics should be given as soon as possible, most critically within 1 hour of presentation. The initial antibiotic choice is an antipseudomonal beta-lactam agent (which should be tailored based on clinical picture). A thorough infectious investigation should be pursued (Algorithm 58.2).
- With SL, cytoreductive therapy is paramount. Induction chemotherapy should be given immediately. For those who are asymptomatic and unable to receive chemotherapy, hydroxyurea (50–100 mg/kg/day orally) is given. For those who are symptomatic and unable to receive chemotherapy, leukapheresis is used.

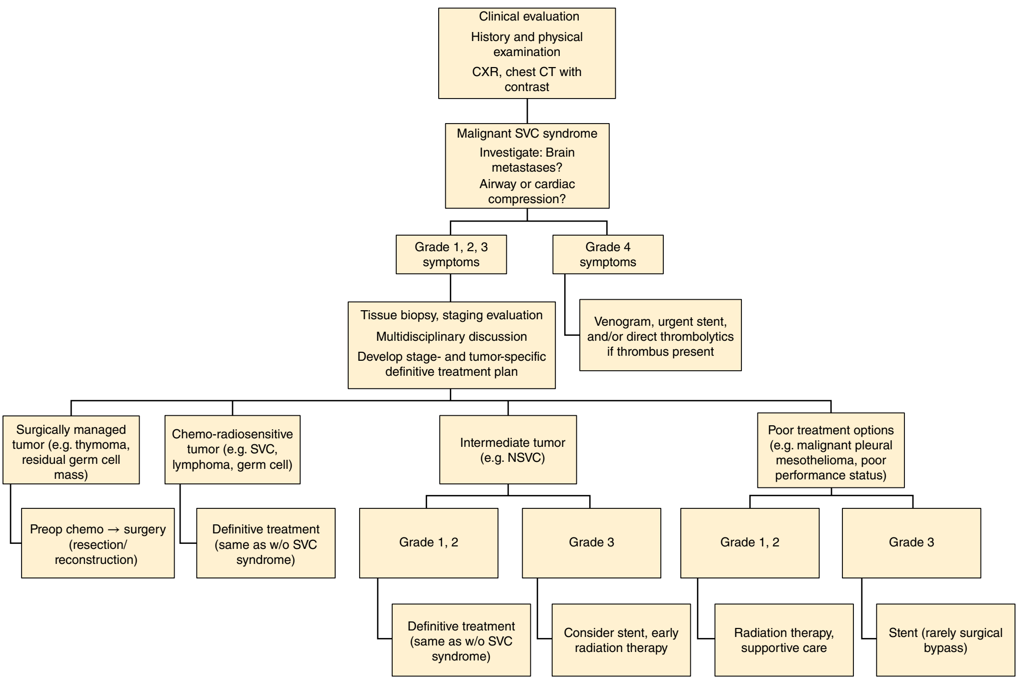
When to admit to the ICU

- TLS and SL are medical emergencies and typically warrant emergent hospitalization.
- Neutropenic fever may warrant ICU admission when symptoms of sepsis are present.

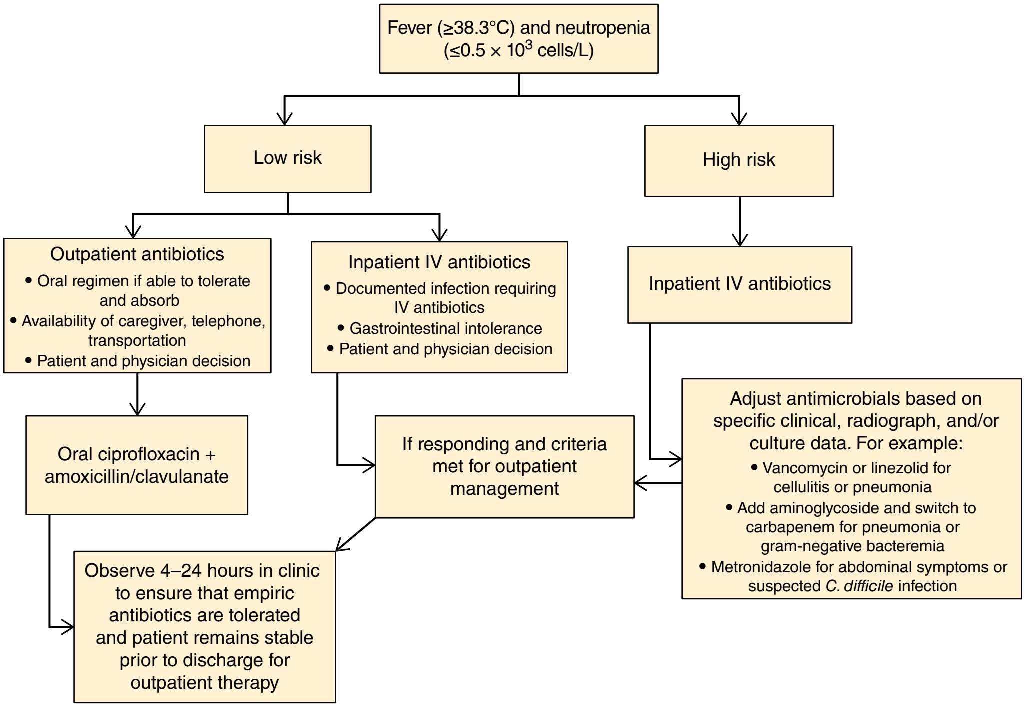
Table of treatment

Disease	Treatment
Tumor lysis syndrome	*Conservative*: The best treatment is prevention including continuous cardiac monitoring, serial labs (electrolytes, renal function, uric acid) every 4–6 hours, and rasburicase 0.2 mg/kg with repeated dosing as needed in high risk patients *Medical*: The management of TLS remains largely supportive with management of electrolyte abnormalities, aggressive hydration, and renal replacement therapy as indicated
SVC syndrome	Combination of conservative, medical, surgical, radiological methods
Neutropenic fever	*Medical*: Broad-spectrum antibiotics should be given as soon as possible, most critically within 1 hour of presentation. Initial antibiotic choice is an antipseudomonal beta-lactam agent (which should be tailored based on clinical picture). A thorough infectious investigations should be pursued *Surgical*: If any abscess is identified, it should be drained. Any indwelling catheters or hardware thought to be the source of infection should be removed immediately
Symptomatic leukostasis	*Medical*: Cytoreductive therapy is paramount. Ideally, induction chemotherapy is given immediately. For those who are asymptomatic and unable to receive chemotherapy, hydroxyurea (50–100 mg/kg/day orally) is given. For those who are symptomatic and unable to receive chemotherapy, leukapheresis is used

Algorithm 58.1 **Management of SVCS**



Algorithm 58.2 Management of neutropenic fever



Prognosis

Prognosis for treated patients

- The in-hospital mortality in neutropenic fever is approximately 10%. If critically ill, mortality increases to as high as 50%.
- The initial mortality rate for AML and leukostasis is 20–40%. If patients survive initially, they generally have lower rates of remission.

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Guidelines

National society guidelines

Title	Source	Date and reference
Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients With Cancer: 2010 Update by the Infectious Diseases Society of America	Infectious Diseases Society of America	2011 Clin Infect Dis 2011;52(4):e56
Recommendations for the Evaluation of Risk and Prophylaxis of Tumour Lysis Syndrome (TLS) in Adults and Children With Malignant Diseases: An Expert TLS Panel Consensus	TLS Expert Panel	2010 Br J Haematol 2010;149(4):57

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